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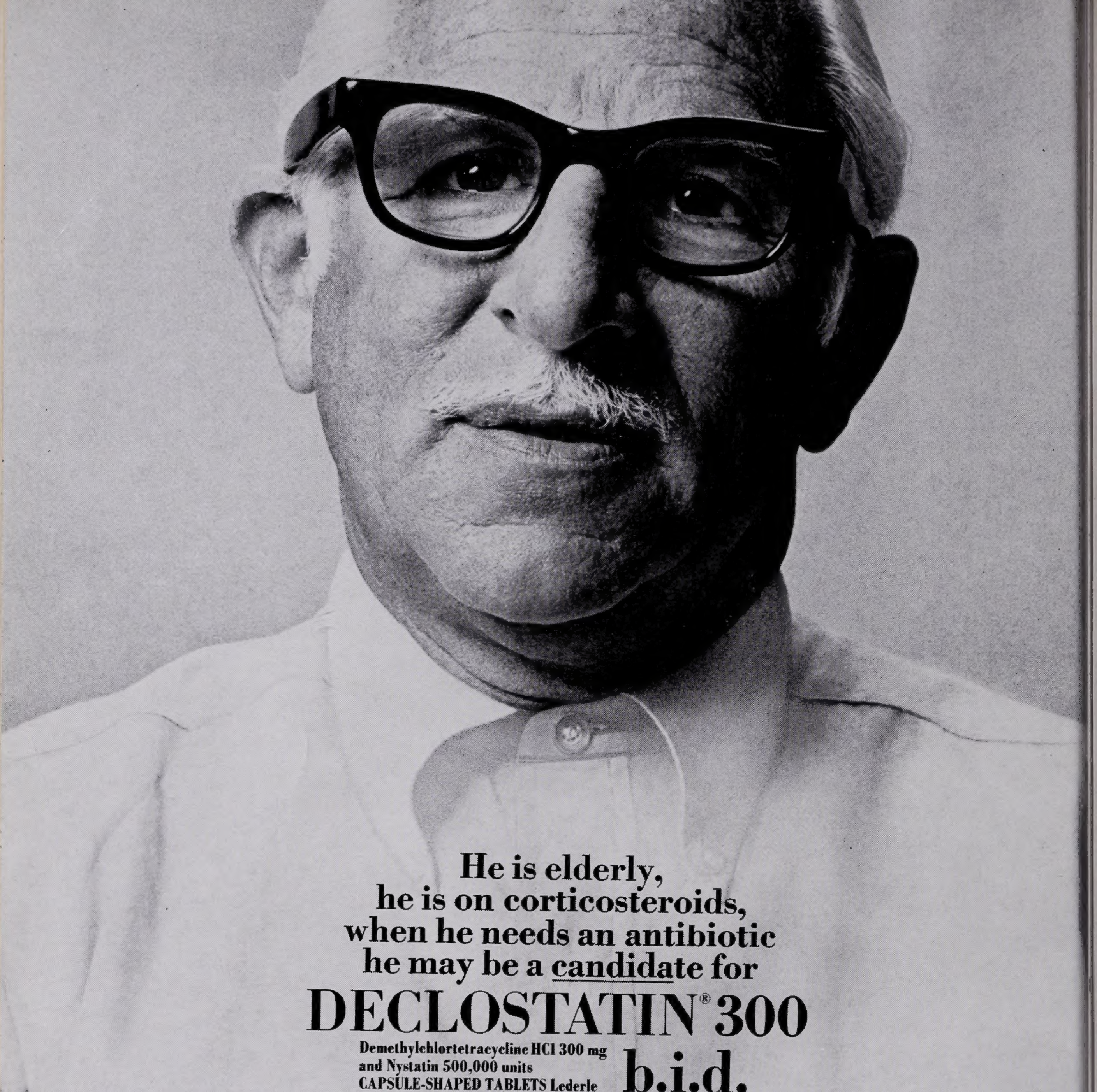

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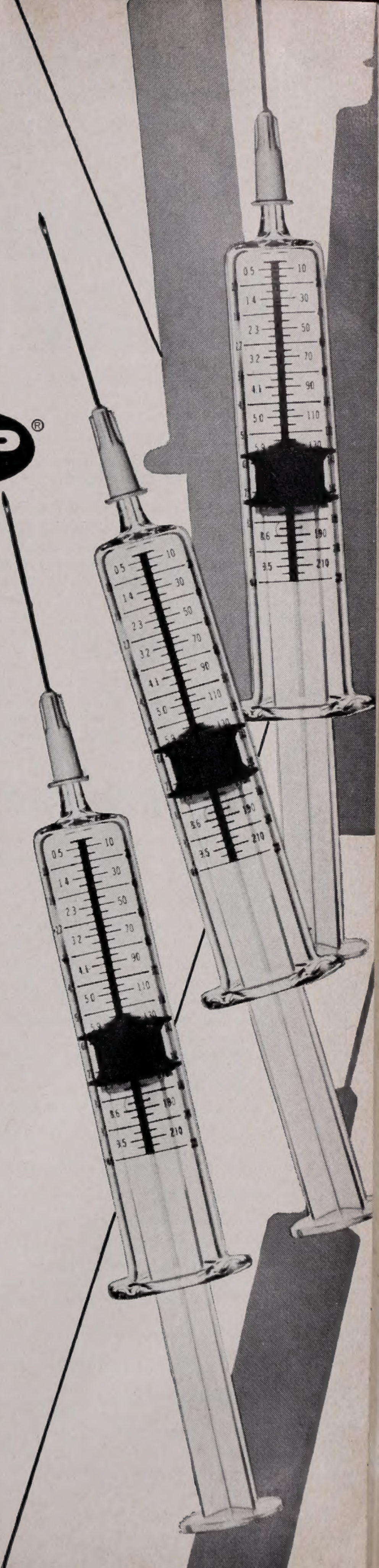

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See the President's Letter, Page 7.

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President's Letter

George E. Fahr, M.D. (1882-1968)

Emeritus Professor of Medicine, University of Minnesota

In early December of last year, our medical community lost one of its mighty men—Doctor George Fahr, a colorful teacher, a gifted researcher, and a respected clinician. To many he was "The Chief" at the old Minneapolis General Hospital. Doctor Owen H. Wangensteen used to liken Doctor Fahr's coming to Minnesota to "opening the window of a smoke-filled room." As we welcome our Swiss friends to these pages, it is only fitting that we dedicate this issue to Doctor Fahr, who loved Switzerland so dearly.

In his memoirs Doctor Fahr relates that he first visited Switzerland as a child in 1893. Later, as part of his extensive training on the continent, he went in 1914 to Berne. There he associated with Leon Ascher, in whose physiology laboratory Doctor Fahr demonstrated how to gild finely-drawn quartz strings with gold. He met the great Kocher but declined to become a surgical resident. He participated in the discussions in Herman Sahli's clinic, much delighting the students with his *schimpfen* (scolding). A lifelong friend was Ery Luescher with whom Doctor Fahr climbed mountains and went skiing. Other well-known names were recalled: R. Staehelin, Loeffler, Bing, and de Quervain.

One of the earliest of the many famous Swiss-born physicians was Paracelsus (Einsiedeln 1493), a controversial figure and for a few years Professor of Medicine at Basel (1527). His was a revolutionary influence on medicine and pharmacy and is best remembered as an advocate of the use of mercury (also sulfur, lead, antimony, iron and copper). He urged surgeons to practice asepsis—"do not touch wounds, because they cure themselves; it is the external agents which complicate processes of cicatrization." He severed bonds with the past, burning the works of Galen, Avicenna, and Averroes. He is quoted as having said, "I pleased no one but the sick whom I cured." More appropriate to this occasion, he also said, "If you really wish to learn, listen to what I say; attend to what I write."

In that spirit, we honor Doctor Fahr's memory and greet our Swiss friends today.

O. L. N. Nelson, M.D., President
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Cover Photo:

The old town of Berne, viewed from the "Rose Gardens," a municipal park, in the direction from East to West.

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The Genesis and Therapy of the Trigger Finger*

K. LENGGENHAGER, M.D.†
Berne, Switzerland

THE TRIGGER FINGER which snaps or jerks at active or passive movements constitutes a typical example of those "minor" ailments which are of considerable practical importance. If the optimum treatment is not applied, the trigger finger can cause the patient much discomfort, and a good many working hours may be lost.[1] The genesis of the trigger finger will therefore be discussed and a simple operative procedure described which has been consistently satisfactory in our hands.

Etiology

Disregarding those rare cases which are caused by osseous changes, three different mechanisms have been proposed as a cause of the trigger finger observed in adults:

Stenosis of the Flexor Tendon Sheath

Stenosis of the flexor tendon sheath with localized pressure on the tendon[2,3,7] seems an unsatisfactory explanation for the etiology as continuous pressure on the tough tendinous tissue would certainly lead to necrosis followed by relaxation. To circumvent this theoretical contradiction, Hauck[2] assumed that the indurated tendon sheath would be indented during flexion and thus produce a stenosis in this situation only (Figure 1). Personal observations suggest, however, that neither of these theories is correct. As a rule, snapping of the finger persists if the finger is kept extended in the metacarpophalangeal joint while being simultaneously and maximally extended and flexed in the interphalangeal joints.

Stenosis and Thickening

The combination of localized stenosis of the tendon sheath and thickening of the tendon itself, which was proposed by Lapidus and Fenton[5] as well as by other authors, for the

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†Professor of Surgery and Chief of the Department of Surgery, University of Berne School of Medicine, Berne, Switzerland.

*See editorial page 81.

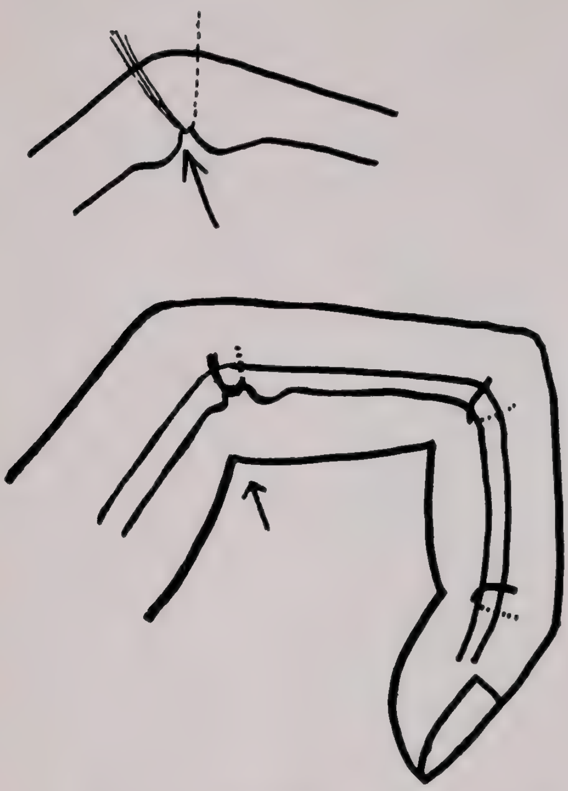

Fig. 1—In this presentation the snapping would occur only in flexion of the metacarpophalangeal joint which does not correspond to reality.

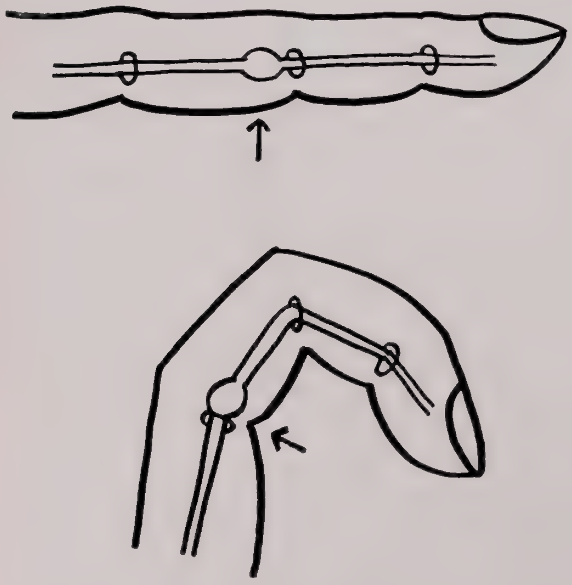

Fig. 2—At extension the club-shaped thickening of the tendon is not at the site of operation. It appears only at active flexion. This position corresponds to the closing of a hand around an object.

reasons outlined above also appears to be a questionable etiologic factor.

Thickening of Tendon

The circumscribed, club-shaped thickening of the flexor tendon[4,9] as a causative factor agrees with our experience accumulated during the past decades.[6,8]

Divergent Opinions

The divergent opinions encountered in the literature and suggesting alterations of the tendon sheath as a cause of the trigger finger may be explained by the following personal observations:

Tendon Thickening Not Visualized

Trigger fingers are usually operated upon from the volar side with the fingers extended. Under these conditions the thickenings of the flexor tendons are not visible after slitting the sheaths and, for this reason, the tendons are presumed to be normal. If, however, the operation is done under local anesthesia and the patient is requested to bend his finger actively, the club-shaped thickening of the tendon will appear with maximal flexion only. This is exactly the position in which the tendon is pressed against the hard, protruding metacarpophalangeal joint while passing through its sheath when the fingers are closed around some hard object (Figure 2). When operation is performed under general anesthesia, the thickening of the tendon cannot be visualized by passive movements of the finger, just as the snapping cannot be demonstrated by passive flexion and extension.

There is yet another reason which argues against the snapping caused principally by the sheath. If a series of model experiments with encircling wires is done on the claws of a dead chicken, it will be observed that a tremendous pressure on the flexor tendon is required to produce snapping when the proximal stump is pulled. In fact, the encircling pressure must be so great as to lead invariably to rapid necrosis of the tendon in the living animal. One person alone will not succeed in tying a single knot of the wire around the tendon tightly enough to produce snapping. The loosening of the first knot despite a continuous pull on the wire ends while the second knot is being tied suffices to defeat the purpose. A jerk will be obtained only if an assistant pulls the tendon stump while the sheath is kept under maximum compression by a continuous pull on the first knot. If the experiment is repeated with a wire sling which is progressively twirled, a jerk may again be obtained with maximum compression of the sheath. Once elicited, however, a double and even triple jerk will be registered when the tendon stump is pulled and the claw subsequently extended to the full. By contrast, in our clinical experience the finger snaps only once when bent or extended and almost regularly with the same degree of flexion. For these reasons, the theory implicating the tendon sheath as the primary factor seems to be of more theoretical than practical interest.

Mechanism of Sensitive Tendon Sheath

Why then is the area around the metacarpophalangeal joint of the trigger finger sensitive to pressure during the clinical examination, regardless of the position of the finger rather than the tendon thickenings themselves? By extending a finger passively, the latter are pulled distally. They are much less sensitive to pain than the better innervated tendon sheaths which are irritated each time the thickening tendon squeezes through. Hence they attain a state of hypersensitivity with or without secondary swelling. The tendon and its sheath are pressed more firmly against the protruding metacarpophalangeal joint when a hard object is grasped than against the more distally located finger joints. For that reason, too, blisters develop over the proximal finger joints after unaccustomed work and not more distally. The thickening of the irritated tendons may thus be compared to that of a clavus.*

Effect of Blunt Trauma

The absent irritation of the skin is hardly astonishing if we consider the frequent occurence of internal damage to muscles, blood vessels and nerves without superficial injury. It is common experience that a blunt trauma preferentially affects the innermost soft tissue areas bordering the underlying hard bone. Well-known examples are the division of the radial nerve following a blow against the lateral side of the arm, intimal rupture of the femoral artery caused by blunt trauma to the inguinal region, the contusion of muscles following a blow against an extremity, and the intestinal and mesenteric lacerations often occuring after blunt abdominal trauma.

Frequently, the snapping of the trigger finger is more pronounced and also more painful in the morning than later in the day. We may deduce that a reparative, sterile inflammatory edema is present at first, which is massaged away as the fingers are moved; hence the space available for the thickened tendon to pass through progressively increases. This interpretation is supported by an observation made on a colleague of mine: A trigger finger of recent origin may disappear completely and spontaneously if an intelligent and cooperative patient will scrupulously avoid active movements and thus keep the finger from snapping for about three weeks.

Diagnosis

The following features are useful for the diagnosis of a trigger finger: If fingers two to

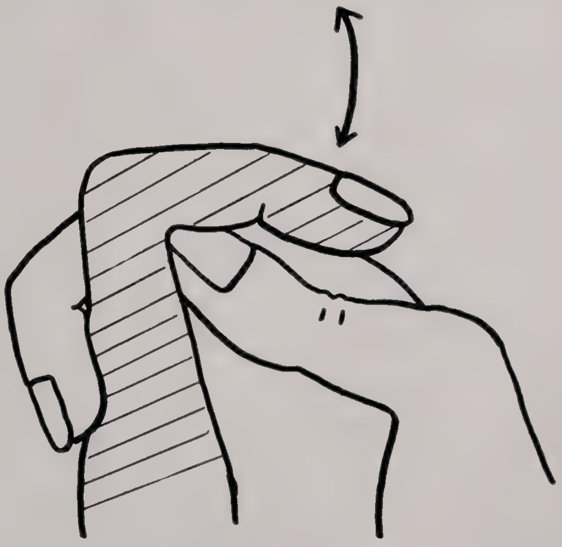

Fig. 3—A test for the existence of a localized thickening of the tendon is the snapping of the finger which is extended in the metacarpophalangeal joint, whereas in the distal joint it is actively bent and straightened.

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*See Test Your Word Score Page 89.

five are bent and straightened actively while the metacarpophalangeal joint is kept extended, a single jerk occurring repeatedly with the same degree of flexion shows a club-shaped thickening of the tendon to be present (Figure 3). Slight volar pain over the metacarpophalangeal joint belongs to the clinical picture. In the case of the thumb, the isolated flexion of the interphalangeal joint will not suffice to induce snapping, because the thickened tendon will not reach the middle joint. Both joints must therefore be moved to elicit the trigger phenomenon.

Therapy

In our experience, a trigger finger of recent origin may disappear completely within three to four weeks if active movements are scrupulously avoided. This phenomenon might be compared to the rapid disappearance of a clavus not maintained by external stimuli.

A simple, "semi-operative" treatment for established cases of trigger finger is the transcutaneous stab incision under local anesthesia proposed by us in 1964.[6] Once introduced through the skin, the slender tenotome moves under the skin only and slits the tendon sheath at the location of pain. All subcutaneous movements should be done strictly lengthwise in the direction of the tendon so as to avoid oblique or even transverse injuries. The sheath is slit further in both directions until the active snapping disappears.

In the case of fingers two to five, the procedure is simple. We do not recommend treating a snapping thumb that way until some experience has been gained with the flexor sheaths of the other fingers, which are more easily found.

No suture is necessary; a small protective dressing suffices. After 10 to 18 days, the patient can close the fist without pain. Up to now we have treated 15 patients with uniformly good results. The first case was operated upon 12 years ago.

Summary

The observations and experiments recorded clarify the divergent opinions about the genesis of the trigger finger and favour the circumscribed thickening of the flexor tendon itself. Conflicting views may be explained by the fact that the club-shaped thickenings of the tendon move into the region where the sheath is slit at operation only when the fingers are actively flexed. Thus they remain unnoticed when the operation is performed under general anesthesia. Their localization corresponds to the region which is chronically irritated when the fingers are closed around some hard object. Experimentally, a single or even multiple snapping can be elicited by placing a wire sling around the flexor tendon sheath of a chicken's claw, but the pressure required would be intolerable in vivo and produce rapid necrosis of the tendon. A simple method of operative treatment is suggested: the tendon sheath is slit subcutaneously under conduction anesthesia with a slender stab scalpel. No suture is necessary.

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Ambition

If you aspire to the highest place it is no disgrace to stop at the second, or even the third.—Cicero

Treatment of Tetanus

A 50-Year Review*

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During the past fifty years (1918-1967) 217 recorded cases of tetanus were treated at the University of Berne Surgical Clinic. This number does not represent the total incidence of tetanus for these years as some records of the first years were lost. This report presents a comprehensive review of the incidence and treatment of tetanus over the past half century at the University of Berne Surgical Clinic.

Incidence

Table 1 shows the age distribution and mortality of our patients for three age groups: It can be seen that the incidence of tetanus in our adult classification has diminished in recent years. This decrease is probably the result of a massive active immunization program carried out by the army since 1940. Relative to the decrease was an increase in the older adults, who never became part of the immunization program.

The sex distribution of the incidence of tetanus from 1918-1967 is shown in Table 2. The ratio of males to females has diminished from 3.3 to 1 (1918-1955) to 1.4 to 1 (1956-1967). This decrease in males could reflect the immunization programs described above.

Treatment

The 100 cases of tetanus recorded during the period (1918-1955) were treated with either $MgSO_4$, chloroform, morphin, avertin or barbiturates.

Since 1956 the severe cases were treated with curare-Succinylcholine 28 cases; d-tubocurare 30 cases; Alloferin® and artificial respiration 19 cases, while the moderate cases (40) were treated with sedatives or valium® (Diazepam).

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*Treatment at the Surgical Clinic, University of Berne, Switzerland.

See editorial page 87.

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Skeletal Muscle Relaxants

In the early cases the muscle relaxants were administered in much higher doses and the patients maintained in complete relaxation. Succinylcholine and curare were given as a continuous infusion in 0.9% NaCl or 5% glucose solutions. Succinylcholine was replaced later by curare and Alloferin® because of tachyphylaxis and excessive bronchial secretion.

Alloferin® is now given intravenously in much smaller, repeated doses (five - 20 mg every 15 to 30 minutes). Complete relaxation is avoided and the drug is administered only when the patient begins to move his face and fingers. Such movements do not interfere with artificial respiration.

The treatment with muscle relaxants (77 cases) was continued for five to 26 days (mean = 13 days). Normal breathing occurred spontaneously one to three days after the last dose of curare. The use of an antagonist such as prostigmin was not necessary.

Treatment of Hypokalemia

Some of our first curarized patients had to be ventilated because paralysis lasted up to 22 days after termination of curare or Succinylcholine. Muscle activity returned very slowly, beginning in face, hands and feet and moving proximally toward the trunk. These patients did not have normal muscular control. Later analysis showed, however, that most had developed severe hypokalemia. These long periods of irregular muscular control after curarization disappeared when potassium was controlled and replaced regularly.

Artificial Respiration

Artificial respiration was given manually in early cases, and later by machine respirators (type Engstrom, Lundia). The respiration is monitored by the rebreathing method (Capnograph Godart[1] and occasionally by blood gas analysis. Before these controls were instituted, many of our patients, particularly children, became chronically hyperventilated. This was the cause of the hyperventilation syndrome and of severe lesions of the central nervous system in some patients.

Hyperventilation Syndrome

In 10 children (two to 16 years) we observed the following syndrome sixteen times: dilatation of the pupils (without reaction to light), edema of tongue and face, salivation, tachycardia (140-180) and marked hypertension. The pressure of the cerebral-spinal fluid increased to 30-40 mm Hg, and a carotid angiogram in one case showed edema of the brain. In this patient with partial curarization, an epileptic state was observed.

The causes for the damage to the central nervous system by hyperventilation are:

1. Constriction of arterioles in the brain

TABLE I

Age Distribution and Mortality

	1918-1967			1918-1955			1956-1967		
	Number of pat.	Died		Number of pat.	Died		Number of pat.	Died	
Total	217	100	46.0%	100	57	57.0%	117	43	36.7%
moderate	71	13	18.3%	31	4	12.9%	40	9	22.5%
severe	146	87	59.5%	69	53	76.8%	77	34	44.1%
2-15 years	68	32	47.0%	35	21	60.0%	33	11	33.3%
moderate	12	1	8.3%	6	0	0%	6	1	16.6%
severe	56	31	55.3%	29	21	72.4%	27	10	37.0%
16-49 years	64	21	32.8%	41	18	43.9%	23	3	13.0%
moderate	27	1	3.7%	15	0	0%	12	1	8.3%
severe	37	20	54.0%	26	18	69.0%	11	2	18.1%
50 years and over	85	47	55.2%	24	18	75.0%	61	29	47.5%
moderate	33	11	33.3%	10	4	40.0%	23	7	30.4%
severe	52	36	69.2%	14	14	100%	38	22	57.8%

with hypocapnea.

2. Impaired dissociation of oxy-hemoglobin with alkalosis of the blood.
3. Edema of the brain by alkalosis of brain tissue and positive pressure respiration (increased venous pressure).

The only effective treatment of this syndrome was hypoventilation with pure oyygen for several minutes. The symptoms disappeared in 30-60 minutes. Two children died a short time after this complication, and the autopsy showed malacia of the brain. Two other children later developed epilepsy. We did not analyze for blood gas or pH in these cases, but since our artificial respiration was later controlled by capnograph and gas analysis, this complication never occurred again.

Homologous Serum

Since 1965 we have used homologous serum (Tetuman^{R} Berna) rather than heterologous serum. The patient is given 250-500 I.U., half by continuous I.V. infusion, half by intramuscular injection. Using this procedure, we had no fatalities in nine severe and 16 moderate cases. Although this data appears highly significant, it still does not prove the superiority of homologous to heterologous serum; in rabbits the homologous antitoxin therapy was not superior to heterologous antitoxin.[2] Many other factors relating to improved management and care of these patients influenced the improved results obtained over the past two years.

Passive-Active Immunization

We have combined serum therapy with active immunization (immunisation simultanée). In a different site from the serum injection, 1 ml of anatoxin (Toxoid) or ½ ml of Anatoxal (adsorbed Toxoid) was given intramuscularly or subcutaneously. After heterologous antitoxin injection, the simultaneous immunization was followed by an interval of about 15 to 25 days without detectable antibodies. This phase occurred between the passive and active immunization. Because of the long half-life of homologous antibodies, no antibody-free interval was detected.

The advantages of the use of homologous

TABLE 2

Sex Distribution

	1918-1955	1956-1967	1918-1967
Male	77	68	145
Female	23	49	72
	100	117	217

TABLE 3

Site of Entry

	1918-1955	1956-1967	1918-1967
Posttraumatic	90	77	167
Postoperative and puerperal	4	1	5
"Idiopathic"	6	39	45
	100	117	217

TABLE 4

Diagnosis in 35 "Missed Cases"

Lumbago	5
Rheumatism	5
"Spasm"	6
Pharyngitis and angina	6
Abscess of tongue and dent. diff.	5
Central nervous disease, brain tumor	3
Torticollis	3
Stupor	1
Meningitis	1
TOTAL	35

TABLE 5

Serum Therapy and Mortality

		Number of Cases	Died	
Heterologous serum	0-5000 I.U.	34	12	35.2%
	6000-19000 I.U.	42	25	59.5%
	20000 I.U.	56	25	44.6%
		132	62	46.9%
Homologous serum	250- 500 I.U.	25	0	0%

serum in the treatment of tetanus are the absence of anaphylactic or other allergic reactions, a continued presence of antibodies and perhaps a lower mortality.

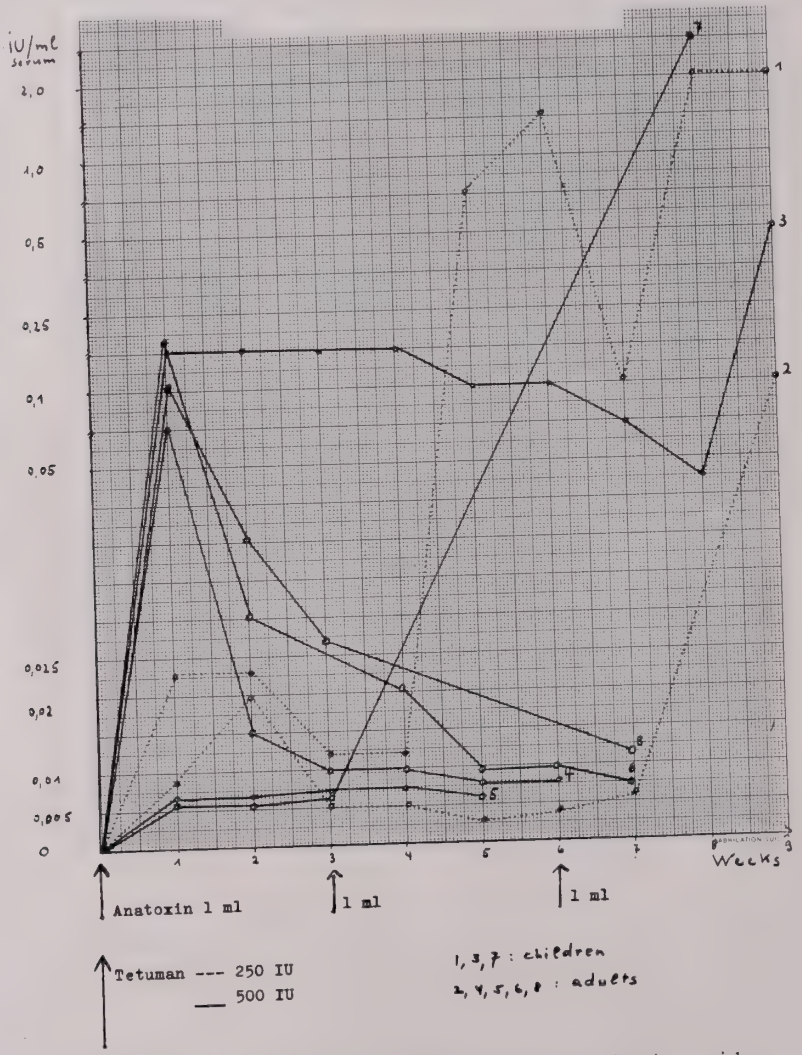
Antitoxin

The figure shows the titers of antitoxin in the blood of eight patients after simultaneous immunization with 250 or 500 I.U. Tetuman® and anatoxin. The titer was higher in children and the level appears proportional to the amount of injected antitoxin. The figure shows that the ideal dosage to yield a continuous titer higher than 0.01 I.U./ml blood, would be 500 I.U. for children and 1000 I.U. for adults. It is of interest that in some of these patients, the titer did not rise after the second or even after the third injection of anatoxin. After six months some patients had a titer of less than 0.005 I.U./ml blood; however, all patients showed a normal and prompt booster effect after 1 ml of anatoxin. In therapy involving simultaneous use of homologous serum and anatoxin, three injections of anatoxin followed by a booster dose after six months are strongly advised.

Miscellaneous Treatment

We did not use *hyperbaric oxygen,* because we could not demonstrate its effectiveness in rabbits.[3]

Antibiotics were used therapeutically to combat pneumonia or other septic complications. Prophylactic use did not diminish septic com-



Figure—Blood titers after simultaneous vaccination with anatoxin and homologous serum.

plications.

Tracheotomy was performed in all 77 patients given curare therapy and in 13 of the 40 moderate cases. There were 20 complications from the tracheotomy: 19 in patients with artificial respiration and one in a patient without artificial respiration. The complications found were:

Bleeding	6
(2 fatal from truncus brachiocephalicus)	
Stenosis in trachea	5
Ulcus in trachea	4
Retracted skin scar	4
Abscess	1

Nutrition

The feeding of a tetanus patient by a thin gastric tube is extremely important. Intestinal peristalsis is reduced in a curarized patient by direct action of curare on the muscles of the gut and by lowered intraabdominal pressure. This curare effect results in delayed emptying of the stomach and in vomiting. In nine patients, oral feeding was prohibited; these patients needed more blood- and- plasma transfusions during treatment. Six of the nine patients developed acute peptic ulceration of the stomach and duodenum. Four of the ulcers perforated and two had repeated bleedings. These complications were avoided when a light diet and antacids every two hours were given.

TABLE 6

Cause of Death

1918-1955 (57 deaths)	
Pneumonia	23
Cardiac arrest during convulsions	19
Asphyxia during convulsions	6
Hyperthermia	6
Pneumothorax	1
Edema of the lungs	1
Aspiration from fracture of base of skull	1
1956-1967 (43 deaths)	
Pneumonia	15
Cardiac arrest	14
Sepsis	5
Embolism of the lungs	2
Lung-abscess	2
Bleeding from tracheostoma	2
Hyperventilation syndrome	2
Endotoxin shock by infected plasma transfusion	1

Results

Mortality

Table 1 shows the overall mortality (1918-1955) to be 57%. The more recent patients (1956-1967) showed a decreased mortality of 36.7%. In severe cases, treated with curare and artificial respiration, mortality diminished from 76.8% to 44.1%. In mild cases the mortality has increased from 12.9% to 22.5%. This increase can be ascribed to the increased number of older patients. For older patients, even mild tetanus, without convulsions, is often fatal. Many died of cardiac arrest and autopsy revealed atheromatosis of the coronaries.

The cause of death is shown in Table 6. The high incidence of pneumonia (1918-1955) was related to the inability of the tetanus patient to expectorate. Cardiac arrest or asphyxia occurred during the dreadful convulsions.

Septic and Cardiac Complications

In the more recent group (1956-1967), septic and cardiac complications still remain important causes of death. Pneumonia is no longer a factor of impaired expectoration, but occurs from hospital infection during treat-

TABLE 7

Mortality in Relationship to Incubation Time and Period of Onset

		1918-1955			1956-1967		
			Died			Died	
Incubation time	3-10 days	50	38	= 76 %	41	10	= 24.3%
	11-20 days	29	12	= 41.4%	22	6	= 27.2%
	> 20 days	7	1	= 14.2%	10	3	= 30.0%
Length of period of onset	2 days	63	50	= 79.3%	47	16	= 34.0%
	3-4 days	15	5	= 33.3%	27	8	= 29.6%
	> 4 days	15	1	= 6.6%	42	19	= 45.2%

ment. Prophylactic use of antibiotics did not diminish the frequency of pneumonia; however, most important in the prevention of pneumonia is the technique of respiration: regular aspiration of mucus by means of a sterile catheter and change of the position of the patient to avoid atelectasis.

Cardiac Arrest

Cardiac arrest occurred in 14 patients. Ten were older than 50 years (six of them were mild cases). Autopsy, in every case, revealed sclerosis of coronary arteries. Four of the patients with cardiac arrest were younger than 11 years; they had severe tetanus and acute myocarditis.

Prognosis

Incubation time and length of period of onset were good criteria for prognosis before the use of curare (Table 7). A short incubation time and period of onset was usually followed by severe tetanus. Because the early patients before 1956 died of anoxia during the convulsions, these cases had a high mortality; with curare treatment the convulsions are no longer a direct cause of death. Other complications, septic as well as some relating to the new techniques of treatment (bleeding from stoma, hyperventilation, perforation of peptic ulcer), may be fatal. Therefore the criteria of period of onset and incubation time have lost their prognostic value.

The age of the patient, however, is significant for the prognosis (Table 1). The middle-aged patient has the best prognosis; the child has a little less favorable prognosis, and the older age group (50 years and over) has the highest mortality.

Convalescence and Invalidism

Follow-up studies of the 38 living patients from 1956-1964 (24 curarized, 14 non-curarized) demonstrated that some had a long convalescence and that *restitutio ad integrum** was not always present.

LENGTH OF CONVALESCENCE	CURARIZED	NON CURARIZED
0-1 month	8	7
1-3 months	3	4
3-6 months	3	2
6-12 months	3	1
Invalidity (25-100%)	7	0
	24	14

The invalidism was caused by: fatigue, muscle pain, weakness in five adult patients, and epileptic fits in two boys (after hyperventilation syndrome).

Enzymatic Changes in Tetanus

During 1964 and 1965 the serum activities of several enzymes were studied in 20 patients. The serum activity of creatine-phosphokinase was elevated upon admission to hospital but, during the next two weeks, progressively de-

TABLE 8

Tetanus Cases after Different Methods of Prophylaxis

Number of Patients	Died	Excision of wound	Antibiotics (Penicillin, Streptomycin)	Serum	Anatoxin (1 Inject., no "rapid" immunization)
11	6	+	—	—	—
2	0	—	+	—	—
2	1	—	—	+	—
7	1	—	—	—	+
2	2	+	+	—	—
1	0	+	+	+	—
1	0	+	+	+	+
1	1	—	+	+	—
4	1	+	+	—	+
1	0	+	—	+	+
2	0	+	—	—	+
1	0	—	+	—	+
35	12 = 34.2%				

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*See Test Your Word Score Page 89.

clined.

Lactate dehydrogenase activity was increased at the time of admission and remained so during the entire stay in hospital.

Activity of alphahydroxybutyrate dehydrogenase was increased from the ninth to the twelfth day in the hospital.[4,5]

Prophylaxis

There are different methods of prophylaxis against tetanus in an injured non-immunized person: excision of the wound, antibiotic therapy, serum therapy, and eventually rapid immunization with anatoxin. These four methods may be used singly or in combination. None is ideal and can guarantee against the outbreak of tetanus.

Thirty-five of our 217 tetanus patients had prophylaxis (see Table 8).

Tetanus after complete active immunization is extremely rare. We have, however, observed the following case: In 1962, a fifty-one-year-old man, previously vaccinated against typhoid, paratyphoid, and tetanus, presented with a contaminated forehead wound. After five days, a mild tetanus, limited to the facial nerve, developed but healed after injection of 1 ml anatoxin.

Discussion

Methods of treatment have changed several times in the last five decades: from morphine to chloroform to $MgSO_4$ and later to barbiturates. Experience with machine respirators, gained in polio patients, was later applied to the treatment of severe cases of tetanus. Finally, total curarization and artificial respiration[6,7] evolved as a therapeutic measure. In moderate cases, Valium® was used with success.

Every new method brought new hope for doctor and patient in the fight against this dreadful disease. Garland[8] wrote in 1959: "With modern methods of treatment nobody dies of tetanus." Unfortunately, with increasing experience this initial optimism was followed by pessimism, expressed in 1935 by Miller:[9] "Treatment in general is hardly more satisfactory than when Hippocrates handled the cases at the battle of Salamis." However, curare therapy represented real progress in treatment of severe cases; patients no longer suffer from painful cramps and the lethality has been reduced.

But this new method of treatment was not without specific complications.

Tracheotomized and ventilated patients were very prone to infections of airways and lungs and apt to succumb to bleeding from the stoma.

Oral feeding of a curarized patient is difficult because of lack of peristalsis; nevertheless, it is very important. The curarized patient does not swallow saliva. If he is not fed by means of a gastric tube, gastric acid is not neutralized for days, and gastric or duodenal ulceration with bleeding or perforation may result. Pelloja[10] suggested central nervous origin of peptic ulceration in tetanus; but we consider it more the consequence of absent neutralization of stomach acid. With antacids and nutrition peptic ulcers were no longer seen in our patients.

Artificial respiration must be controlled by a rebreathing method[11] or by blood gas analysis. The dangers of hypoventilation are well known and can be avoided. Hyperventilation may be equally dangerous, especially in children, who may develop the hyperventilation syndrome.[12,13]

Small series of patients with good results do not prove the superiority of any special therapy. Kloetzel,[14] who treated 52 patients with a total mortality of 42%, found a consecutive series of 19 patients without mortality. We too had no mortality in our last 25 cases. We feel that this improvement is due not only to the homologous serum used in this series, but to other factors such as improved techniques of nutrition, artificial respiration and patient care.

Fatality will never be reduced to zero in tetanus patients, as long as there is only a symptomatic therapy, because specific complications like tetanus-myocarditis cannot be prevented.

Since Ramon,[15] there has been great progress in immunological understanding and treatment of tetanus. However, today little is known of the pathogenesis of the disease.[16] Hopefully new enzymological methods may further knowledge.

Summary

From 1918 to 1967, 217 cases of tetanus

were treated in the Surgical Clinic of the University of Berne.

The use of curare lowered the mortality rate from 57% to 37%. In recent years an idiopathic type of tetanus, without detectable wound, has become prevalent.

During the last 12 years, 77 severe cases were curarized and given artificial respiration. Monitoring of ventilation to prevent complications such as the hyperventilation syndrome is important. Potassium replacement is also indicated. Regular tube feeding is advocated to prevent peptic complications. Moderate cases can be successfully treated with Valium® (Diazepam).

Heterologous serum in high doses did not affect mortality. In 25 cases treated with homologous serum there was no mortality.

Pneumonia, other septic complications, and cardiac arrest are still the prevailing causes of death. Prophylactic use of antibiotics did not diminish septic complications.

Tetanus is often followed by long convalescence and invalidism.

Creatine phosphokinase, lactate dehydrogenase and alphahydroxybutyrate dehydrogenase are elevated in tetanus. Thirty-five of the 217 cases had prophylaxis after injury. The safest means of preventing tetanus in a injured patient is through active prophylactic immunization.

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Etymologically Speaking*

Lank from Anglo-Saxon *hlank*—flexible.

In Arkansas there still remains some Old English, retained since Elizabethan days. After a strenuous morning of gastrointestinal X-rays and no food the patient remarked that he was "lank."

The term had been used by Milton: "Her lank head" and by Swift: "Meager and lank with fasting grown."

Webster gives the synonyms: slender, shrunken, languid, etc. In colloquial Arkansas use, however, it means all pooped out and awfully hungry.

Raymond C. Read, M.D.
Little Rock, Arkansas

Derivatively Speaking*

Cretin—from French *cretin,* a dialectal term for Christian, from Latin *christianus.*

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*Derivatively speaking refers just to word origins; Etymologically speaking also includes word development and historical changes in meaning.

Cardiac Metabolism in Experimental Hemorrhagic Shock*

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HEMODYNAMIC ALTERATIONS recorded by several authors show that cardiac deterioration occurs in prolonged experimental hemorrhagic shock. Whether or not myocardial function constitutes the crucial parameter for the progression of shock towards irreversibility remains a matter of dispute. Electrocardiographic and histological changes indicating subendocardial damage have been repeatedly observed. Besides unspecific necrotic foci, a presumably characteristic kind of "zonal lesions" involving fragmentation of myocardial cells was recently described by Hackel's group.[11]

The metabolic basis of cardiac deterioration in hemorrhagic shock remains to be elucidated. An insufficient oxygen supply was suggested by earlier findings pertaining to the oxygen tension in coronary sinus blood and to alterations of lactate/pyruvate metabolism. Another possible cause of myocardial depression might be alterations of enzyme activities, whether due to hypoxia, to excessive catecholamine activity producing structural derangements within the heart muscle,[3] or to some toxic substance(s) of extracardiac origin,[6] which might be produced in peripheral tissues damaged by shock-induced hypoxia. Combinations of such mechanisms might, of course, well be operative.

Our laboratory has been interested in cardiac metabolism during hemorrhagic shock for some time, and the results obtained so far will now be presented briefly. For the details and fuller bibliographies, we may refer to more extensive reports published in specialized journals.[7-10]

Oxygen Supply of the Heart in Hemorrhagic Shock

Direct measurements of tissue oxygen tension in the beating heart are technically ex-

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acting, not easy to interpret, and demand equipment and experience available in a limited number of specialized laboratories. A relatively simple and sufficiently accurate technique consists in sampling coronary sinus blood and determining its oxygen saturation. The oxygen tension can be monitored directly or calculated from the percent saturation and pH. The percent oxygen saturation and oxygen tension of venous blood from the heart reflects the situation of cells deriving their oxygen supply from the venous end of capillaries, which are most likely to suffer an oxygen deficit. A number of studies reveal that the "critical" oxygen saturation or oxygen tension of coronary sinus blood below which lactate output indicates myocardial anaerobiosis is very low, less than 10% or 10 mm of mercury, respectively. Thus the essential question is whether that level is attained during hemorrhagic shock.

In shock studies on previously healthy, open-chest dogs maintained on constant artificial ventilation, the coronary sinus oxygen level under control conditions depends to a considerable extent upon the ventilation employed. With high control levels, oxygen saturation declines significantly during shock, whereas with low control levels, there is hardly any change. This is illustrated by Figure 1 which shows the behavior of the coronary sinus oxygen saturation in two series of experiments performed in our laboratory.

In neither study was the critical level of coronary sinus oxygen saturation (or oxygen tension) attained. If we assume that the changing balance between coronary perfusion pressure and cardiac workload basically tended to restrict myocardial oxygen supply under the hemodynamic conditions of shock, coronary vasodilation compensated sufficiently for this to prevent an oxygen deficit of the heart.

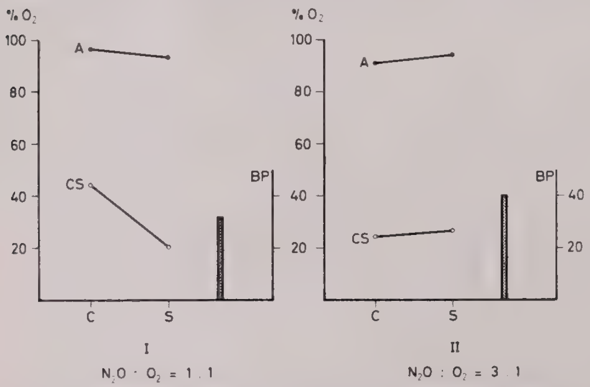

Fig. 1—Arterial and coronary sinus percent oxygen saturations in two series of experiments with shock blood pressures of 32 mm (I) and 40 mm of mercury (II). Gas mixture in series I $N_2O : O_2 = 1 : 1$; in series II, $N_2O : O_2 = 3 : 1$. A= arterial, CS = coronary sinus, C = pre-shock control, S = shock.

What are the clinical implications of these findings? With arterial oxygen saturations above 90%, coronary vessels capable of responding adequately to incipient tissue hypoxia and a normal oxygen transport capacity of the blood, an oxygen deficit of the heart during hemorrhagic shock does not appear to be relevant. Conversely, a substantial degree of arterial hypoxemia—due, for instance, to obstructed airways or thoracic trauma—and preexisting coronary disease may well produce a critical degree of coronary sinus desaturation. This may also result from excessive hemodilution with erythrocyte-free artificial colloids; circulatory improvement equals an increase in cardiac workload and thus of myocardial oxygen consumption, which must be covered by a reduced oxygen transport capacity of the blood. Cardiac oxygen extraction, which is already high under normal conditions may thus become excessive and produce a critically low saturation or oxygen tension on the venous side of myocardial capillaries. Altogether, then, adequate ventilation is mandatory, excessive hemodilution must be avoided, and the coronary patient is particularly susceptible to myocardial damage during shock.

The evaluation of myocardial oxygen supply by the analysis of coronary sinus blood is complicated by the fact that gradients of oxygen tension exist within the normal heart.[5] The oxygen tension in the subendocardial layers is only about half that recorded in the outer layers of the left ventricle. If such gradients persist during shock with oxygen saturation and oxygen tension in the "average" coronary sinus blood approaching the critical threshold, they might cause a subendocardial oxygen deficit escaping detection by the analysis of blood draining hypoxic as well as non-hypoxic areas of the left ventricle wall. This problem will be dealt with later.

Lactate/Pyruvate Metabolism

From present knowledge, alterations of

myocardial lactate and pyruvate metabolism may be considered the most sensitive indicator of a cardiac oxygen deficit. The normal heart muscle extracts lactate and pyruvate from the blood in proportion to their arterial concentrations. Under the conditions of pure arterial hypoxemia, the critical threshold of coronary sinus oxygen saturation and tension is revealed by the change of the myocardial lactate balance from uptake to output. As stated before, it equals saturations of 10 – 5% or an oxygen tension of 10 – 5 mm of mercury.

Another approach is the analysis of the lactate/pyruvate ratio in arterial and coronary sinus blood. This ratio is in fact a redox quotient, and it is usually slightly lower on the venous side of the heart, indicating oxygen supply of the myocardium to be adequate. Under conditions probably inducing excessive catecholamine activity, it may be slightly higher in coronary sinus blood in the face of oxygen saturations not suggesting a deficient supply. With pure arterial hypoxemia, the lactate/pyruvate ratio in the coronary sinus rises above that of arterial blood entering the heart in proportion to lactate output, and an evaluation of the critical threshold of the coronary sinus oxygen saturation produces the same results with both parameters. During shock, alterations of the lactate/pyruvate ratio may become equivocal because prolonged shock tends to induce a myocardial output of pyruvate which is probably not related to oxygen supply per se.

The myocardial extractions of lactate and pyruvate were studied in our laboratory simultaneously with the parameters of oxygen supply illustrated in Figure 1. In the first series of experiments with a mean blood pressure of 32 mm of mercury during shock lasting for a maximum 1½ hours, myocardial output of lactate was registered in about one third of the samples. In nearly every instance, however, there was a concomitant output of pyruvate. For this reason, the average change of the lactate/pyruvate ratio across the heart did not suggest the presence of a myocardial oxygen deficit.

In the second series, shock was maintained at 40 mm of mercury until the animals had taken up one third of the maximum blood volume lost into the reservoir, or an average 5¾ hours. During the final stages of this shock period and with the coronary sinus oxygen saturations depicted in Figure 1, there was a consistent uptake of lactate and nearly always output of pyruvate. The decrease of the lactate/pyruvate ratio across the heart was therefore accentuated in the shock state. Thus the alterations of lactate/pyruvate metabolism during prolonged hemorrhagic shock at 40 mm of mercury confirmed the impression obtained from the behavior of coronary sinus oxygen parameters that an oxygen deficit does not contribute to the cardiac deterioration regularly observed following retransfusion in studies of this type. As judged from the results of the first series, however, a blood pressure approaching 30 mm of mercury may create borderline conditions with respect to myocardial oxygen supply.

It is suggested that studies designed to evaluate cardiac performance in shock should include an analysis of oxygen saturations and lactate/pyruvate metabolism in arterial and coronary sinus blood. This would facilitate comparison of results obtained with different blood pressure levels and respiratory conditions selected by various authors for such investigations.

For the analysis of lactate and pyruvate in coronary sinus blood, the problem of a non-uniform metabolism of heart muscle cannot be neglected. Besides the gradient of oxygen tension between the superficial and the deep layers of the left ventricle, Honig found the lactate/pyruvate ratio to be 28 in the outer and 34 in the inner layers. The oxygen and lactate/pyruvate gradients thus run in opposite directions and fit the concept of a higher glycolytic activity in the subendocardial layers of the left ventricle wall under normal conditions. It is entirely conceivable that such gradients may be important in shock.

Enzyme Activities in Left Ventricular Myocardium

Recent studies on frog sartorius muscle suggest that enzymatic activities may adapt themselves to alterations of contractile activity within a matter of hours. Furthermore, characteristic activity changes of certain glycolytic enzymes were established in the guinea pig heart when heart-lung preparations were subjected to increasing workloads or hypoxemia to the point of cardiac failure.[12] Both kinds of stress produced the same alterations; myocardial hypoxia was therefore regarded as their common cause. These findings suggested an approach to the problem of metabolic gradients within the heart in the normal state and during shock, which has recently been explored in our laboratory.[9,10] Briefly stated, the procedure is as follows.

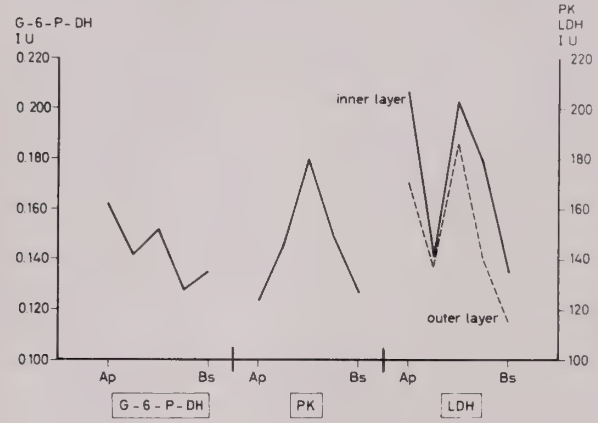

Fig. 2—Enzyme activity gradients in the direction from apex to base of left ventricle following shock. Maximum-minimum differences for each enzyme significant with $p < 0{,}05$.

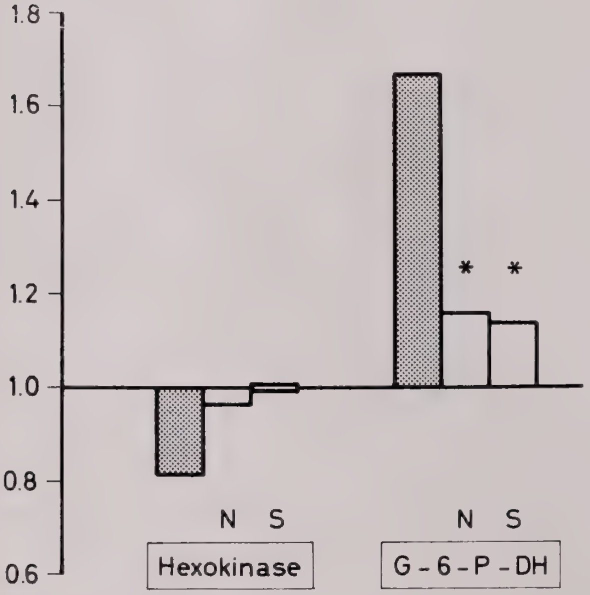

Fig. 3—Activity ratios "cardiac failure (hypoxia) / control" (hatched columns) from Hochrein's data[12] and activity ratios "inner layer/outer layer" of left ventricle wall (open columns) in present study. N = normal state, S = post-shock state, * = significantly different from unity with $p < 0{,}05$. Hexokinase and Glucose-6-Phosphate Dehydrogenase.

The metabolic status of the heart was monitored in one series of 12 dog experiments during a 2½-hour period of presumably normal working conditions as judged by conventional oxygen, lactate/pyruvate and acid-base parameters in the blood. In a second series of 12 experiments with identical ventilation, the same blood parameters were studied during the final stages of a 5¾-hour shock period at 40 mm of mercury and following retransfusion. At the end of these experimental periods, the heart was excised in toto.

Myocardial samples were taken from five sampling sites in the direction from apex to base of the left ventricle. From each sampling site, the tissue was divided into one portion each from the inner and the outer third of the left ventricle wall. In addition, three samples from papillary muscle were secured from each animal. The following enzymatic activities were assayed in each tissue sample: hexokinase, glucose-6-phosphate dehydrogenase, fructose-1,6-diphosphate aldolase, glyceraldehyde phosphate dehydrogenase, pyruvate kinase, lactate dehydrogenase, alpha-hydroxybutyrate dehydrogenase, isocitrate dehydrogenase and malate dehydrogenase. The results were subjected to statistical analysis by means of a two-way analysis of variance and significance tests (F-test and t-test). In this way, the activity differences between animals, sampling sites, and inner and outer layers of the left ventricle wall could be assessed.

Significant activity differences were found among animals for all enzymes in the normal state and following shock; but they will not be further considered here.

In the normal state there were no significant activity differences or gradients between sampling sites, i.e., in the direction from apex to base of the left ventricle. Following shock, however, such gradients appeared in the inner layer of the left ventricle wall for G-6-P-DH, pyruvate kinase and lactic dehydrogenase. For the latter enzyme, the activity differences between sampling sites were also significant in the outer or subepicardial layer. As seen from Figure 2, the general trend was for the enzyme activities to rise in the direction from base towards apex of the left ventricle.

The picture was irregular, however, and suggested a functional disorganization afflicting the subendocardial layers preferentially.

Figures 3 to 5 illustrate two groups of activity ratios. The activity ratios "cardiac failure/control" calculated from Hochrein's data[12] are shown as hatched columns. A ratio in excess of one denotes that the activity of the enzyme in question rises with cardiac failure due to workload or hypoxia, the latter supposedly being the common denominator for both conditions. Similarly, a ratio less than one denotes a falling activity of the enzyme in question under such conditions of "stress."

The columns designed as "N" and "S" show the activity ratios "inner layer/outer layer" found by us in the normal state and following shock.[9,10] A ratio in excess of one denotes a higher activity in the inner layer, and vice versa. GAP-DH and alpha-HB-DH were omitted in these Figures, because no data were available from Hochrein's study[12] with which they might have been compared.

Let us first compare the ratios "cardiac failure (hypoxia)/control" to the normal ratios "inner/outer layer." It is seen that with the exception of IDH, their deviations from unity are concordant. Without exception, the activity ratios "papillary muscle/outer layer" (not shown in Figures 3-5) were also concordant with the ratios "inner/outer layer", reflecting the essentially comparable situation of the subendocardium and papillary muscle and showing the same agreement with Hochrein's data.[12] These findings suggested that a permanent metabolic adaption to a restricted oxygen supply might exist in the subendocardial layers of the normal left ventricle,[9] in accordance with the differences of oxygen tension and the lactate/pyruvate ratio reported by Honig.[5]

Second, let us compare the activity ratios "inner layer/outer layer" found in the post-shock state with the other two. With the exception of lactic dehydrogenase and MDH, they change in a direction opposite to that presumed to reflect a restricted oxygen supply. The strict concordance between the ratios "inner/outer layer" and "papillary muscle/outer layer" observed in the normal state was disrupted for several enzymes following shock, among them for lactic dehydrogenase (I/O > 1,0; P/O < 1,0).

On the whole, therefore, the behavior of the enzymes studied does not support the assumption of an overall oxygen deficit of the myocardium during shock, nor does it suggest the presence of a hidden subendocardial oxygen deficit which might escape detection by an analysis of coronary sinus blood. When considered together with the activity differences between sampling sites affecting mainly the subendocardial layers, the alterations of the transmural activity gradients in the post-shock state suggest a functional disorganization of the myocardium at the cellular or subcellular level.

With the lack of evidence for an oxygen deficit, which factors may be invoked to ex-

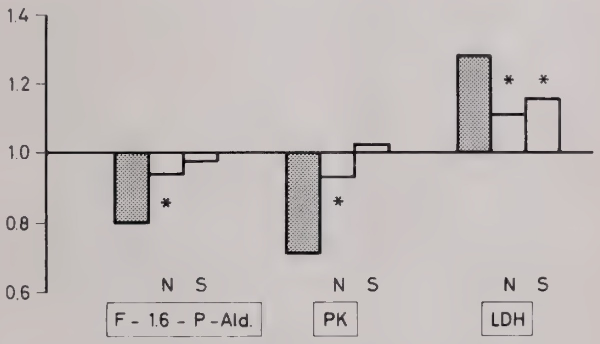

Fig. 4—Activity ratios as in Figure 3, for fructose-1,6-diphosphate aldolase, pyruvate kinase and lactate dehydrogenase.

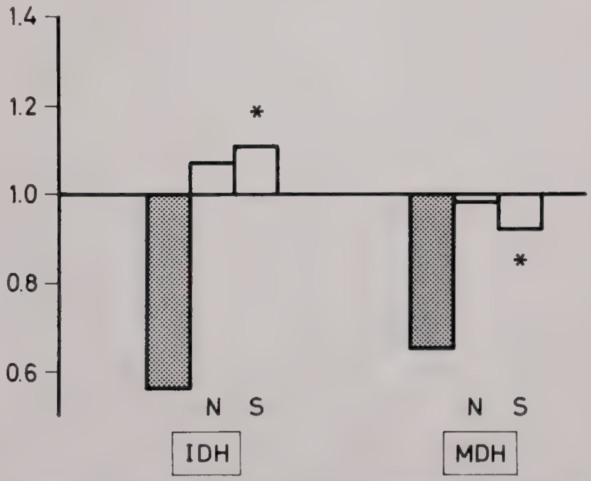

Fig. 5—Activity ratios as in Figures 3 and 4, for isocitrate dehydrogenase and malate dehydrogenase.

plain a functional disorganization of the myocardium following prolonged hemorrhagic shock? A reasonable assumption would be that it is related to the structural derangements predominating in the subendocardium in the postshock state. From experiments with beta receptor blockade in shock, it has recently been inferred that such structural derangements might be related to excessive catecholamine effects.[3] Experiments designed to shed further light on this mechanism are currently in progress in our laboratory. In the meantime, we have found that β-receptor blockade by propranolol does in fact abolish the activity gradients between sampling sites found in "untreated" shock (Figure 2). Excessive catecholamine effects thus appear to be involved.

Another possible mechanism would be myocardial depression by some toxic substance(s) arising in hypoxic peripheral tissues during shock.[6] They might interfere directly with cardiac metabolism or indirectly by way of structural alterations probably occurring at the subcellular level. Disturbances of cellular ultrastructures have recently been described in vascular smooth muscle, striated muscle, liver and kidney following shock[1,4] and it has been suggested that such changes might induce alterations of enzymatic processes.[2] As a working hypothesis, the findings reported here may be interpreted as an example of such relationships between cellular or subcellular disturbances of myocardial structure and function due to prolonged hemorrhagic shock.

Summary

The metabolic basis of cardiac deterioration following prolonged hemorrhagic shock remains to be elucidated. Under experimental conditions as usually employed for the study of such relationships, neither the parameters of myocardial oxygen supply nor those of cardiac lactate/pyruvate metabolism suggest that impaired performance of the otherwise intact heart following shock might be due to an oxygen deficit. The study of activity distribution patterns of several glycolytic enzymes within the left ventricle wall of the dog heart furnishes no evidence of a hidden subendocardial oxygen deficit during hemorrhagic shock when arterial oxygen saturations remain above 90%, coronary vessels are healthy, and the oxygen transport capacity of the blood is normal. Definite alterations as compared to the normal state are, however, recorded. They are interpreted to suggest a functional disorganization of the myocardium at the cellular or subcellular level, which might be connected with structural derangements due to excessive catecholamine activity or with the effects of toxic substances produced by peripheral tissues during shock.

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11-12. May be secured from the author.

I have finally come to the conclusion that a good reliable set of bowels is worth more to a man than any quantity of brains.—Josh Billings

Hypoxia and Renal Function

A Review of Experimental and Clinical Findings

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Early in this century the mechanisms of acclimatization to high altitude in man were studied by several groups of physiologists.[6,8] This for the first time drew attention to changes in renal function after transition into a hypoxic environment. Investigations were mostly concerned with homeostasis of acid-base components. Some of our present knowledge on acid-base metabolism is, in fact, founded on these observations. After arrival at altitude, diminution of plasma bicarbonate content was observed which had to be explained by renal bicarbonate loss. More recently Relman et al.[16] demonstrated the dependence of renal tubular bicarbonate reabsorption on plasma carbon dioxide tension which is low during hypoxic hyperventilation at high altitude. Increased renal bicarbonate elimination under such circumstances appears to involve a tubular $Na^+ - H^+$ exchange mechanism and is therefore accompanied by sodium diuresis.[19]

Since methods are available to estimate renal glomerular filtration rate and effective renal plasma flow acute hypoxia has been shown to elevate these two parameters.[3]

Effect of High Altitude

In permanent high-altitude residents, on the other hand, glomerular filtration rate and, more so, the effective renal plasma flow were found to be significantly below the range of sea-level values.[12] This finding is even more marked in patients with chronic mountain sickness.[10] The tendency for sodium and fluid retention in these patients stands in contrast to the above mentioned sodium diuresis in the beginning of exposure to hypoxia. Direct comparison of sea-level residents with permanent high-altitude dwellers, however, makes interpretation difficult, as many regulatory and metabolic factors have to be taken into account which might develop over months, even years of high-altitude residency or be active before or at birth in such an environment. Observations of changes in renal function during the first days of exposure of sea-level residents to high altitude had to fill this gap.*

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Sea-Level Dwellers

Eight healthy sea-level dwellers have recently been observed before and during a 10-day sojourn at 3454 meters above sea level.[1] Among many physiological and biochemical measurements glomerular filtration rate and effective renal plasma flow were estimated by radioisotope-disappearance techniques as well as renal handling of sodium, chloride and potassium by the classical clearance methods.[15] During this high altitude period changes in renal handling of electrolytes (Figure 1 a and b) were more pronounced, although with a wider scatter than in glomerular filtration rate and effective renal plasma flow (Figure 2). Increased sodium and chloride elimination during prolonged hypoxia appears to involve a tubular mechanism, as is the case for diminished potassium elimination. Changes in glomerular filtration rate and effective renal plasma flow are comparatively slight during this observation period. The mean of all values for effective renal plasma flow, however, calculated for the days seven to 10 is significantly decreased in comparison to control values at the 5% confidence level (Wilcoxon-test). No correlation of these changes with simultaneously determined circulatory parameters in these subjects could be found.[9]

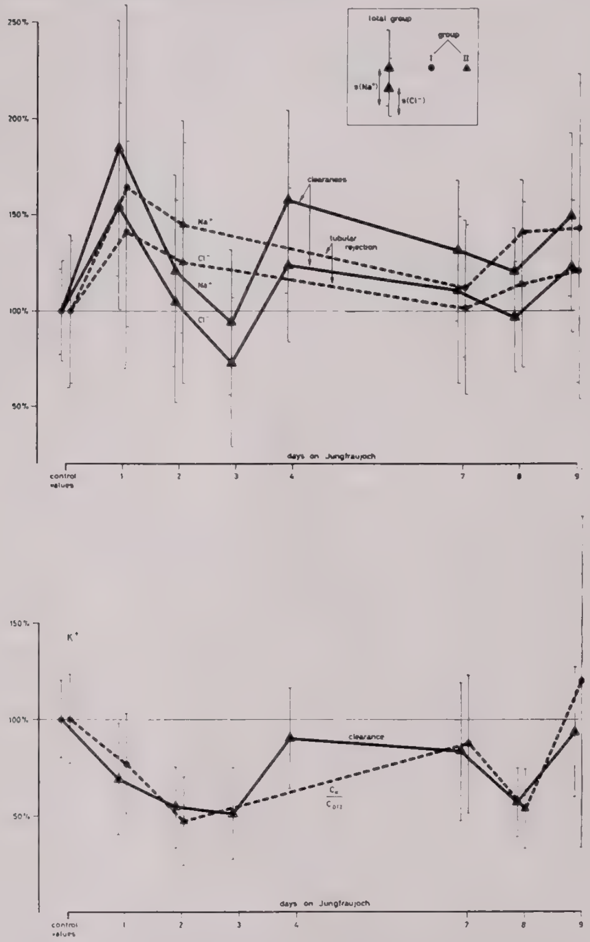

Fig. 1—Renal clearance for sodium, chloride (a-top) and potassium (b-bottom) in eight healthy sea-level residents (Copenhagen) before and during a 10-day sojourn at Jungfraujoch (Switzerland). Renal "tubular rejection" is the ratio between electrolyte clearance and clearance of diatrizoate (representing glomerular filtration rate, see Figure 2). All values are related to control data (Copenhagen) which are made to equal 100%. Single standard deviations are indicated (for Na^+ at the left, for Cl^- at the right side of the vertical lines). The mean values for clearances cannot be directly compared with the ones for "tubular rejection" as they include the total group (eight subjects) or the sub-groups I and II (four subjects) on each day respectively.[15]

Chronic Hypoxia

In patients with chronic hypoxia due to pulmonary insufficiency and ensuing cor pulmonale effective renal plasma flow and glomerular filtration rate are diminished.[5,17] Fishman et al.[5] found these values to increase during acute additional hypoxia, while they were further lowered under acute reoxygenation by O_2 inhalation. In the same patients acute additional hypoxia increases and reoxygenation decreases sodium elimination. The observed changes were not found to correlate with changes in cardiac output measured simultaneously.[5] These experiments seemed to indicate that derangements in renal function in patients with cor pulmonale were due to an unknown factor, not identical with hypoxia. On the contrary, hypoxia was assumed to increase effective renal plasma flow from an even lower value (i.e., the level attained during reoxygenation).

At the time of these reports serious objections against O_2 inhalation in patients with cor pulmonale had been raised for other reasons.[4] These reports and the above mentioned findings of Fishman et al.,[5] on the other hand,

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*In the following this type of exposure will be called *prolonged* in contrast to *acute* (exposure up to several hours) and *chronic* (permanent residence at altitude).

seemed to contradict the long known clinical fact that under long-term O_2 inhalation some patients with chronic cor pulmonale exhibit a marked increase in diuresis, followed by disappearance of edema.[2] The results of oxygen administration in such patients seem to depend on the careful observation of acid base components in the arterial or capillary blood of the patients, and to the dosage of oxygen in the inspired air by suitable devices.[2,7,14,17] Under such conditions renal function values tend to change in the *opposite* direction, as under short-term application of high oxygen concentrations in the inspired air.[14] In Figure 3 an example of observations during such a treatment is given.

Comments

The combined experimental and clinical evidence of the influence of hypoxia on glomerular filtration rate, effective renal plasma flow, and renal handling of sodium therefore indicates that one has to distinguish between acute and chronic effects which seem to operate by different mechanisms. *Acute* hypoxia is followed by an increase mainly of effective renal plasma flow, less so of the glomerular filtration rate, of only a few hours' duration, most probably connected with general and renal autoregulatory hemodynamic changes. At the same time tubular sodium reabsorption seems to decrease concomitantly with an elevated renal elimination of bicarbonate, which has been shown to depend on the decrease of plasma pCO_2 during the development of hypoxic hyperventilation. This alteration in renal tubular handling of sodium is therefore not dependent on hypoxia *per se*[18] but on acid base derangements triggered by the hypoxic ventilatory drive and can be observed during *prolonged* hypoxia (Figure 1 a).

Evidence of increased activity of the adrenal cortical and the renin-aldosterone systems[11,13] under such conditions cannot be interpreted as primary but possibly as compensatory to such a derangement in tubular function.

It is doubtful whether renal hemodynamic changes as evidenced by decreased values in effective renal plasma flow and less so in glomerular filtration rate in high-altitude dwellers and patients with chronic cor pulmonale can be explained by general circulatory mechanisms. Sodium and fluid retention in the latter as well as in patients with chronic mountain sickness must depend on other mechanisms than renal sodium handling during acute and prolonged hypoxia. As long-term relief from hypoxia can correct these derangements, a direct metabolic disturbance of renal tubular transport of sodium during chronic hypoxia must be considered.

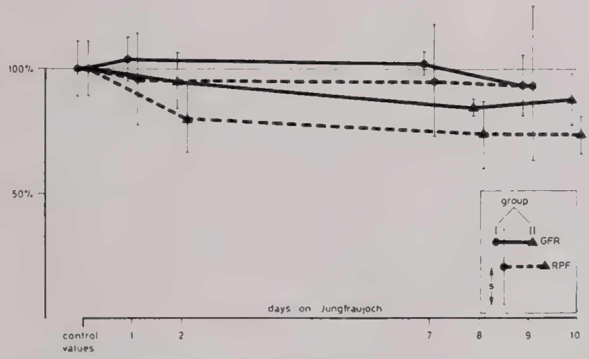

Fig. 2—Mean renal clearances for diatrizoate (glomerular filtration rate = GFR) and orthoiodohippuric acid (effective renal plasmal flow = RPF) before and after ascent to high altitude (same subjects as in Figure 1). The lines connect the mean values of 2 subgroups (I and II; 4 subjects each).[15]

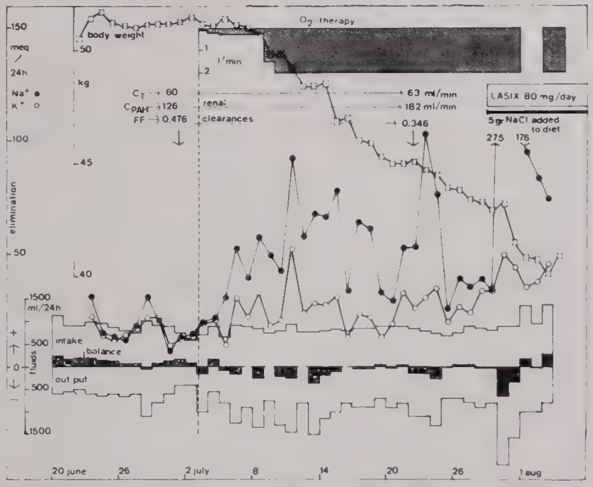

Fig. 3—Fluid balance, renal sodium and potassium elimination, weight change and renal clearances of thiosulfate (C_T = GFR) and paraaminohippurate (C_{PAH} = RPF) in a 63-year-old female with obstructive pulmonary emphysema and congestive heart failure due to cor pulmonale. Diet and all medication were kept constant during the control period and continuous O_2 inhalation through a nasal catheter, except where indicated. Furosemid (Lasix) was given after clinically manifest edema had disappeared.

References may be secured from the author.

The Algebra of Quackery

"Ailment plus medicine equals cure" is an equation widely cherished as true. But the algebra is not so simple. Countless times, of course, the true equation is "Ailment plus Nature equals cure," and if any drug is added its value is zero. Why, a physician once asked, was quackery more prevalent in medicine than in other areas of science? "Because," he answered himself, "the medical quack attributes to himself what is due to Nature. Nature can not build a railway, but she can very often cure disease." Quacks have harvested countless testimonials from customers whose gratitude was thus misplaced.

Another version is this: "Symptoms equal disease," hence, add medicine to produce cure. A vastly confusing aspect of medical science, to physician as well as to layman, is the way so many ailments, major and minor, are heralded by the same symptoms. An Atlanta chest specialist, checking medical textbooks, found 56 different causes for spitting blood, 76 different causes for pain in the chest, 137 different causes for coughing. The quack has taken advantage of such confusion, claiming that his bottled remedy has cured a dread disease at the serious end of the cough spectrum—say, tuberculosis—when in fact a change in the weather has dried up postnasal drip. To the quack and his most susceptible victims, all coughs are consumption, all lumps cancer, all backaches kidney disease.

Since "symptoms equal disease" in the mathematics of credulity, the quack can go a step further in tampering with the equation. He can, through his promotion, substitute false symptoms for real symptoms. He can convert normal physiological conditions, like low spirits, tiredness, mild insomnia, spots before the eyes, into dire harbingers of syphilis and insanity. Therefore, in the patent medicine algebra, "non-symptoms equal disease," ergo, add Helmbold's Extract of Buchu to produce cure.*

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*James Harvey Young: The Medical Messiahs, 1967.

His Nganga* Failed

Dunywa:† was admitted with pain of three months' duration over the upper abdomen. Clinical diagnosis was of a primary carcinoma of the liver. The patient had consulted a diviner, who had declared that his illness was due to his grandmother's spirit, which wanted a beer ceremony and a cloth. At the same time, the nganga had treated him with certain herbs. But although Dunywa had brewed the beer and bought the cloth his health had not improved.‡

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*Nganga—Southern Rhodesian witch doctor.
†Dunywa was admitted to a Southern Rhodesian hospital after his nganga failed to cure him.
‡Michael Gelfand: Witch Doctor, 1965.

After a few years of marriage, a man can look right at a woman without seeing her—and a woman can see right through a man without looking at him.—Helen Rowland

Love does not dominate; it cultivates.—Goethe

Antidiuretic Action

of Chlorpropamide and Tolbutamide

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In the course of studies aimed at assessing the antidiuretic activity of several newly synthesized polypeptides chemically related to the natural antidiuretic hormone of man, we became aware of two reports pointing at antidiuretic hormone-like activity of Chloropropamide,† a drug widely used for treatment of maturity-onset diabetes mellitus.[1-4] Since the antidiuretic effect of Chlorpropamide is of considerable theoretical and practical interest, this drug along with Tolbutamide‡ was further investigated in overhydrated healthy volunteers. Meinders et al. failed to produce antidiuresis in two overhydrated normal subjects given Chlorpropamide p.o. The question of whether or not Chlorpropamide decreases free water clearance only in patients with lack of endogenous antidiuretic hormone and fails to do so in subjects with functionally suppressed antidiuretic hormone release, is of paramount importance for further studies on the mode of action of this drug.

Methods

Eleven healthy male volunteers (aged 20-26), three of them trained in previous experiments, were hydrated by the ingestion of 20 ml water/kg body weight. A steady state of hyperhydration was maintained by the ingestion of an amount of water equal to the volume of urine voided during the preceding 15 minutes. The experimental procedure was started when reasonably comparable urine volumes were voided at subsequent 15-minute intervals. No catheter was used, but the subjects were instructed to empty their bladder completely at exactly 15-minute intervals. All subjects remained in a recumbent position during the whole procedure except for the time necessary to void. A blood sample for measurement of osmolality was obtained through an indwelling venous catheter at approximately the midpoint of the experiment. Drugs were injected through this same catheter. A Fiske osmometer was used for measurements of osmolality in blood and urine samples. All samples had been previously frozen.

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†1—propyl-3-p-chlorobenzenesulfonylurea.

‡1—butyl-3-tolylsulfonylurea.

Since this work was submitted a further important contribution to the problems discussed here has been published: Reforzo-Membrives, J. Moledo, L. I., Lanaro, A. E. and Megías, A.: J Clin Endocr 28:332, 1968.

Osmolal clearance was calculated as $C_{osm} = \frac{V \times U_{osm}}{P_{osm}}$ and Free Water Clearance as $C_{H_2O} = V - C_{osm}$ (V = urine flow in ml/min U_{osm} and P_{osm} = The solute concentration of urine and plasma in milliosmols/kg water).

Experiments A, B, C, F, G, J, K, L, M were started at 8 a.m. in fasting subjects; D, E, H were started at 2 p.m. in subjects having taken a light meal.

Experimental procedures aimed at assessing antidiuretic compounds in human subjects are prone to produce many kinds of artefacts, since the suppression of endogeneous antidiuretic hormone production induced by heavy hydration may be overridden by other stimuli to antidiuretic hormone secretion such as emotional stress (e.g., insertion of needles) or even slight changes of position. Care was taken to avoid such artefacts (see Exp. C and G, where the indwelling needle had to be reinserted). The experimental set-up is illustrated in Figure 1 representing a study on dose-response relationship of Lysine^8-Vasopressine*, Tyrosine^2-Ornithine^8-Vasopressine* and Phenylalanine^2-Isoleucine^3-Ornithine^8-Vasopressine*.

Five hundred mg Chlorpropamide (Diabinese Pfizer), dissolved in 5 ml 0.9% NaCl solution, and 1000 mg Tolbutamide (Artosin Boehringer), dissolved in slightly alkaline solution, were given intravenously. Blood sugar levels were assessed enzymatically at least twice, before and 30 to 40 minutes after injection of the drug. No symptoms of hypoglycemia were noted except possibly in subject H who complained of dizziness 30 minutes after injection of Chlorpropamide.

In one single experiment (A, not illustrated) 500 mg Chlorpropamide were injected in a patient hypophysectomized for diabetic retinopathy three days before. The patient suffered from moderately severe diabetes insipidus. No clearcut acute effect of Chlorpropamide on urine flow was found (osmolality was not measured).

Results

Individual results of six studies with Chlorpropamide are presented in Figure 2.

Chlorpropamide Effect

In three subjects (E, F, G) definite antidiuresis occurred immediately after injection of 500 mg Chlorpropamide. One subject (D) responded only moderately, whereas no antidiuresis occurred in two cases (B and C). Whenever antidiuresis did occur, it was accounted for by a decrease in free water clearance, C_{osm} remaining practically constant.

Lysine-Vasopressine Before and After Chlorpropamide

In Subject B a dose of 0.009 I.U. Lysine-Vasopressine injected before and after Chlorpropamide had almost identical antidiuretic activity. In Case G 0.008 I.U. Lysine-Vasopressine given two hours after Chlorpropamide produced slightly more marked antidiuresis than the drug, although Chlorpropamide antidiuresis lasted longer.

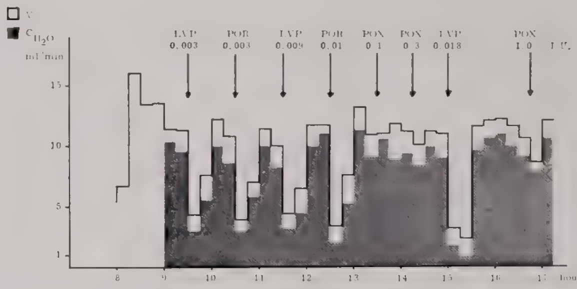

Fig. 1—Experimental protocol used to study the antidiuretic potency of unknown drugs (here designated as Tyrosine-Ornithine-Vasopressine (POR) and Phenylalanine-Isoleucine-Ornithine-Vasopressine (POX); details see section "Methods") in comparison to Lysine-Vasopressine. Effect on urine flow (V, white area) and free water clearance (free water clearance, hatched area). This experiment is illustrated in order to provide data on fluctuations of "steady-state" diuresis, reproducibility and drug specificity of antidiuresis, duration of antidiuresis produced by antidiuretic-hormone-like polypeptides. The drug effects may be compared with those of Chlorpropamide and Tolbutamide (Figure 2 and 3). These latter substances are not suitable for repeat injection.

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*These compounds were synthesized by Sandoz S. A.

Antidiuretic Hormone Effect

The peak antidiuretic effect of Chlorpropamide occurred in four cases (D, E, F, G) within 15 to 30 minutes, just as it does after injection of Lysine-Vasopressine. However, with polypeptides akin to antidiuretic hormone, preinjection steady states were usually reattained within approximately 45 minutes after the injection (see Figure 1; Figure 2, exp. B and G; Figure 3, exp. L), whereas the Chlorpropamide antidiuresis lasted somewhat longer.

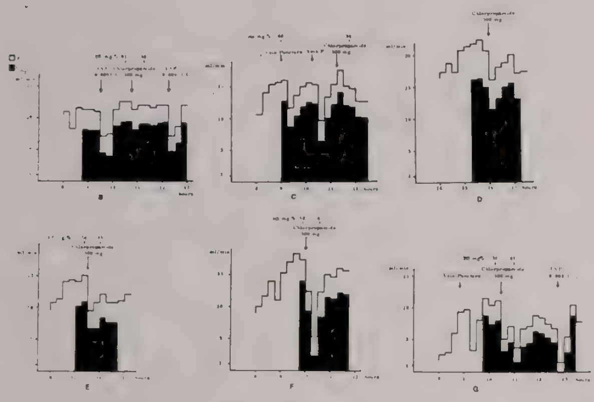

Fig. 2—Effect of 500 mg Chlorpropamide I.V. on urine flow (V, white area) and free water clearance (free water clearance, hatched area) in six subjects. In subjects B and C there was no response. D showed a possible response, whereas definite antidiuresis occurred in subjects E, F and G. Blood sugar levels are indicated when measured. In experiments B and G the effect of Lysine-Vasopressine was also investigated (see text).

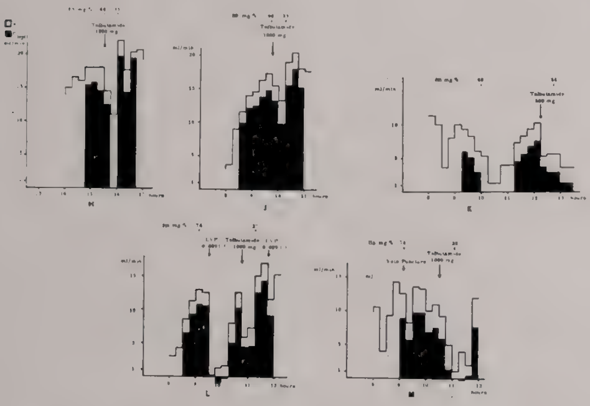

Fig. 3—Effect of 1000 mg Tolbutamide I.V. on urine flow (V, white area) and free water clearance (hatched area) in five subjects. (Note that in experiment H no free water clearance could be measured in the 16-hr. sample. The same is true for the five samples voided between 10 and 11:15 a.m. in experiment K). Definite antidiuresis occurred in subjects J, L and M. H and K gave equivocal results. In K an unexplained spontaneous and transient antidiuresis makes one hesitate to accept the second antidiuresis following the drug's injection as a Tolbutamide-dependent phenomenon. Subject H was disturbed during voiding the 16-hour sample. Blood sugar concentration decreased in all but subject K by more than 10 mg/100 ml.

Tolbutamide

In a further study, Tolbutamide, another antidiabetic drug, was investigated for possible antidiuretic activity (Figure 3). Out of five experiments, Tolbutamide had a definite antidiuretic effect in three, and a possible effect in the other two. Subject H was disturbed by a third person at the very moment of micturation 30 min. after Tolbutamide. We are therefore not sure if the antidiuresis is apparent or really drug-dependent. In subject K spontaneous antidiuresis occurred for no apparent reason after a urine flow of 10 ml/min had been obtained. Again there is some doubt about the specificity of the antidiuresis after this Tolbutamide injection, although the prompt decline in free water clearance speaks in favour of such a relationship.

In subject L a dose of 0.009 I.U. Lysine-Vasopressine was injected before and after Tolbutamide. The effect of the second dose was definitely smaller.

Discussion

Arduino et al. and Meinders et al. have recently reported that Chlorpropamide has antidiuretic properties in patients suffering from diabetes insipidus due to lack of antidiuretic hormone. The drug was ineffective in diabetes insipidus of renal origin and, in the study of Meinders, in two overhydrated normal subjects.

Our studies, carried out in normal human male volunteers previously hydrated to suppress endogeneous antidiuretic hormone secretion, show that Chlorpropamide does induce moderate antidiuresis in some, but not in all overhydrated normal subjects. Previous studies, undertaken in our laboratory in order to establish a dose-response relationship for Lysine-Vasopressine and some newly synthesized related polypeptides, had clearly shown that the minimal effective dose of antidiuretic hormone and its congeners may considerably vary from one subject to another and may not even be constant for a given individual. The inconstant antidiuretic effect of 500 mg Chlorpropamide is thus compatible with the concept that this dose is nearly as effective as a small, borderline antidiuretic dose of antidiuretic hormone (for Lysine-Vasopressine this would be around 0.001 I.U.). Higher doses of Chlorpropamide and Tolbutamide were not used for fear of causing side effects. We do not believe that a dose-response relationship can be obtained in man.

As stated for Chlorpropamide, Tolbutamide also causes slight but definite antidiuresis in hyperhydrated humans.

In diabetes insipidus there is often no need for a potent antidiuretic agent, since even a slight increase of the maximum concentrating power of the kidney may decrease the urine flow to an acceptable level. The clinical usefulness of Chlorpropamide has indeed already been established. However, an antidiuretic activity in overhydrated normal subjects had not previously been observed (Meinders).

No definite answer as to the probable mode of action of the two drugs emerges from these studies. There was no definite correlation between the fall of blood sugar and an antidiuretic effect. Blood sugar concentration dropped in seven out of 10 subjects tested by more than 10 mg/100 ml. Moreover, the two compounds did not potentiate the action of Lysine-Vasopressine (see experiments B and L). It cannot be decided from our studies whether or not the drugs directly stimulate endogenous antidiuretic hormone release or whether they themselves have antidiuretic hormone-like properties.

If the relatively long half-lives of the two drugs (five hrs. for Tolbutamide and 36 hrs. for Chlorpropamide) and their rather short antidiuretic action are taken into consideration, one is tempted to speculate on the antidiuretic action being the consequence of the acute release of endogeneous antidiuretic hormone stores. However, the rather strong antidiuretic effect of Chlorpropamide in diabetes insipidus of central origin is an argument (although not a definite one) against this hypothesis.

Still another possibility should be considered: It is well known that diuretics such as thiazides or ethacrinic acid are of some value in treatment of diabetes insipidus, even in the renal variety of the disease (Brown et al. and Crawford et al.). Thiazides are chemically related to Chlorpropamide and Tolbutamide since most of these drugs belong to the sulfonamide group. Therefore the possibility of a common mode of action should be further explored even if the two cases of diabetes insipidus renalis reported by Arduino et al. did not seem to respond to Chlorpropamide.

Summary

Chlorpropamide, given per os, was recently reported to lower urine flow and to decrease free water clearance in subjects with diabetes insipidus due to a deficiency of antidiuretic hormone, but not in overhydrated normal subjects.

Our studies show, however, that 500 mg Chlorpropamide injected I.V. into overhydrated volunteers induce definite antidiuresis in about half the subjects. The antidiuretic activity of this dose is thus equal, both quantitatively and qualitatively, to a very small dose of Lysine-Vasopressine, which may also fail to induce antidiuresis in some subjects. The qualitative similarity of the antidiuretic effect of Lysine-Vasopressine and Chlorpropamide is all the more surprising as the two drugs have very different biological half-lives. No definite answer as to the mode of action of Chlorpropamide can be given.

It was furthermore shown that Tolbutamide, another antidiabetic drug, has similar antidiuretic properties in overhydrated human volunteers.

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Whenever I feel like exercise, I lie down until the feeling passes.—Robert Maynard Hutchins

Renal Clearances

Comparative Studies of Sodium Thiosulfate and Na_2Cr (Cr^{51}) Ethylenediaminetetracetate (Cr^{51}-EDTA) in Man*

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In the past few years a variety of glomerular markers, tagged with a gamma-ray emitting isotope, have been proposed as substitutes for inulin. Radio-labelled compounds such as C^{14}-carboxylinulin,[1] I^{125}-allyl inulin,[2] CO^{57}-cyanocobolamine[3,4] have been discarded because of expense or other major disadvantages. Good correlation with conventional inulin clearances were reported in rather small series with newer glomerular markers such as I^{131}-sodiumdiatrizoate (Hypaque),[5] I^{131}-meglumindiatrizoate (Renografin),[6] I^{131}-sodiumiothalamate (Conray),[7] I^{125}-iothalamate (Glofil)[8] and Cr^{51} labelled Na_2Cr-ethylenediaminetetracetate (Cr^{51}-EDTA).[9-11]

The enthusiasm for substitutes for inulin will be shared by everybody who struggled along with chemical determination of inulin. One should not, however, sacrifice accuracy for simplicity. We felt that the appropriateness of a glomerular marker could be established only on the basis of extensive correlative studies between the substitute and the two standard glomerular markers, inulin and Na-thiosulfate. Among the new glomerular markers Cr^{51}-EDTA seems to qualify best since this complex is stable in vivo, since Cr^{51} has a very convenient half-life and physical properties, and since it is low-priced.

We have therefore compared simultaneously-determined renal clearances of either Na-thiosulfate or inulin and Cr^{51}-EDTA in a large number of patients. Our results indicate that the clearance of Cr^{51}-EDTA is slightly but definitely below the clearance of Na-thiosulfate and inulin. Still the line of regression defining the correlation of the two clearances may be used as a calibration curve to derive glomerular filtration from the Cr^{51}-EDTA clearance. In this short paper we shall comment only on the results of the Na-thiosulfate series.

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*Supported by the Swiss National Research Grant No 4345.

†Medical Outpatient Department, University of Berne, Switzerland.

Material and Methods

Under standard clearance conditions,[12] we determined in 47 patients with normal renal function or various degrees of renal impairment the clearances of Na-thiosulfate and Cr^{51}-EDTA in 103 clearance periods. Na-thiosulfate determination was performed according to the usual technic in our laboratory.[12] Cr^{51}-EDTA was obtained from the Farbwerke Hoechst, Frankfurt, Western Germany, with a specific activity of 40 μCi/mg Cr. The stock solution contained 1 mCi/ml (corresponding to 180 μg Cr-EDTA per ml), and it was diluted with sterile saline to contain about 50 μCi/ml. 15-20 μCi Cr^{51}-EDTA were added to the priming infusion; the sustaining infusion was made up of 200 ml sterile saline (9%) and of 12-15 μCi Cr^{51}-EDTA. It was infused at a rate of 3 ml/min. After an equilibration period of at least 20 minutes, the urinary bladder was emptied and the first clearance period started. Two to three clearance periods were obtained from each patient.

Great care was taken to maintain plasma levels of Na-thiosulfate above 25 mg%, since it is known that if plasma concentration falls below 25 mg%, the Na-thiosulfate clearance tends to be higher than the inulin clearance.[12] Blood was withdrawn from an antecubital vein with no or only minimal hemostasis and centrifuged at 2000 rounds per minute for 15 minutes to avoid hemolysis. Two ml of plasma and 2 ml of urine were pipetted into plastic counting test tubes (Packard International) and counted in a well-type NaI scintillation crystal. At least 10,000 counts per minute were obtained from each sample. The lower level of the discriminator was set at 280 keV, the upper at 350 keV.

Results

Our results are plotted in the Figure. Each point corresponds to one clearance period. It can be seen that the correlation between the two parameters is very good. The equation of regression runs as follows: $y = 1.066 \cdot x$ ($s_b = \pm 0.0068629$). The 95% confidence limits are indicated by dashed lines. The mathematical model which applies best to the distribution of our data has been taken from M. G. Nutrella.[13] The clearance of Cr^{51}-EDTA was deliberately taken as independent parameter and plotted on the abscissa, since we believe that it can be determined with a smaller technical error than the Na-thiosulfate clearance. The line of regression which follows the equation $y = 1.066 \cdot x$ is significantly different from $y = x$, and it may therefore be used as a calibration curve.

Discussion

Cr^{51}-EDTA can very easily be measured by means of its gamma-ray emission. The low price and the convenient physical properties of Cr^{51} make it a desirable substitute for Na-thiosulfate. Radiation dosage to the patient is trivial since it is of the order of 5 mrad to the kidney in normal individuals with the tracer dose used in this study. No side effects have ever been observed from EDTA. To derive glomerular filtration rate, one has to multiply the clearance of Cr^{51}-EDTA by 1.066. At present we cannot explain the fact that the Cr^{51}-EDTA clearance is slightly lower than the clearance of Na-thiosulfate. Plasma protein binding is of the order of 0.5-2.0%[9,11] and will therefore not fully account for the difference. Recovery for Cr^{51}-EDTA in normal individuals is 95% after 24 hours.[11] We could not find measurable amounts of Cr^{51} in washed erythrocytes 16 hours after the clearance test,

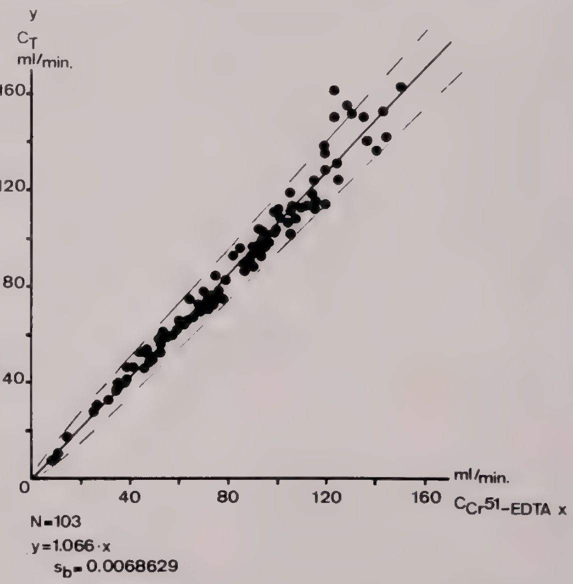

Figure 1—The Na-thiosulfate clearance (y) is plotted against the Cr^{51}-EDTA clearance (x). The line of regression is marked with an unbroken, thick line; the 95% confidence limits for a future value are indicated with dashed thin lines.

so that a split-off of Cr^{51} is very unlikely. Increasing the plasma concentration of Cr^{51}-EDTA 15 times or increasing the urinary volume up to 28.0 ml/min had no effect on the correlation with inulin clearance.[14,15]

Comparison of the renal clearances of Cr^{51}-EDTA and inulin in 181 clearance periods leads to the same conclusion.[14,15] The pattern of correlation is practically the same as in Figure 1, the coefficient of regression being slightly higher, 1.077. On the basis of this study, it seems justified to recommend Cr^{51}-EDTA as a valid substitute for Na-thiosulfate or inulin as a glomerular marker using a mean correction factor of 1.073. Thus the true glomerular filtration rate may be easily and accurately determined by any laboratory which uses a well-type NaI scintillation counter. This technique permits one to overcome the difficulties arising from the time-consuming inulin determination, and should be preferred to the inaccurate single injection method.

Summary

Under standard clearance conditions we have performed in 47 patients with normal renal function and various degrees of renal impairment (103 clearance periods) simultaneous clearances of Na-thiosulfate and Cr^{51}-EDTA. The priming infusion contained 15-20 Ci, the sustaining infusion 12-15 μCi of Cr^{51}-EDTA in 200 ml 0.9% sterile saline, infused at the rate of 3 ml/min. Cr^{51}-EDTA was determined from 2 ml plasma and 2 ml urinary samples, counted in a well-type NaI scintillation counter up to at least 10,000 counts. A high degree of correlation between the two clearances was found, the equation of correlation running as follows: $y = 1.066 \cdot x$ ($s_b = \pm 0.0068629$). On the basis of our results we feel that Cr^{51}-EDTA makes a valid substitute for Na-thiosulfate and inulin as well. The clearance of Cr^{51}-EDTA, however, has to be multiplied by 1.073 to obtain the true glomerular filtration rate.

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Prerequisites for a Physician

The physician should be of tender disposition, of wise and gentle nature, and more especially an acute observer, capable of benefiting everyone by accurate diagnosis, that is to say, by rapid deduction of the unknown from the known. And no physician can be of tender disposition if he fails to recognize the nobility of man; nor of philosophical nature unless he be acquainted with Logic; nor an acute observer unless he be strengthened by God's guidance; and he who is not an accurate observer will not arrive at a correct understanding of the cause of any ailment.*

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*From the Four Discourses by Nizami-i-Arudi, composed A.D. 1155. Persian poet, 12th century.

Marriage is neither heaven nor hell; it is simply purgatory.—Abraham Lincoln

It's the Law

Primer of Parliamentary Procedure*
The Tactics of Delay

At some point in an organized meeting it may become necessary for proponents and/or opponents of a particular action to consider some means of deferring or halting action on a motion, whether for the good of the assembly or for a strategic purpose.

If it is the intent of the assembly to defer action on a motion for a specific period of time, say until the next regular or annual meeting, the proper phrase is: "Mr. Chairman, I move that we *postpone consideration* of this motion till the next meeting." After being seconded and debated, a simple majority of the society may thus defer action for a stated period. This motion, *to postpone to a certain time,* is usually confused with the motion to *lay on the table.* Very frequently, a member will move "to lay this matter on the table until next month," thereby confusing the assembly and often the chair. A prudent chairman, hearing this erroneous phrase, will immediately ask the mover which of the two motions he is proposing, explaining if need be, as a point of order, the difference between the two.

The motion, *to lay on the table,* is another distinct means of deferring action on a particular proposal in order to allow the assembly to attend to more urgent business. The effect of this motion is to place the pending question in charge of the Secretary temporarily, usually until more urgent matters have been disposed of and the assembly is ready to consider new or unfinished business. Properly employed, the motion *to table* defers temporarily, and does not enable a majority to kill a measure instantly (which is the effect of this motion in the U.S. Congress) but preserves the right of a majority vote to *take from the table* those matters deferred at the proper moment during the same or a succeeding meeting.

The motion *to table* has a high priority of entry, must be seconded, but is undebatable. It cannot be qualified by adding a phrase such as "until Friday" or "until the next meeting." A simple majority is necessary for approval of this motion.

Perhaps this lesson should include some brief mention of a motion directed toward avoiding delay, of forcing the assembly to vote promptly on a pending matter. Suffice it to say, then, that the motion "*to close debate* and vote immediately on the pending question" must be seconded and requires a *two-thirds* affirmative vote. Like the motion *to table, to close debate* (move the Previous Question) is undebatable.

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*See Minnesota Med 51:1800, 1968.

We are so vain that we even care for the opinion of those we don't care for. —Ebner-Eschenbach

Every shut eye ain't asleep.—American Negro proverb

Central European Encephalitis ("Tick-borne Encephalitis") in Switzerland

Discussion of Nine Known Cases

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ARTHROPOD-BORNE VIRAL infection (ARBOR-Virus Group B) has been repeatedly described in Europe during the last few years.[1,2,3,6,7,8,9,10,11,13,15,18,20,23,24,26,29,30,31,32,] In general a spreading of the infection from east to west has been established. The occurence in southern Germany has been proven.[25,26] In Switzerland, however, until now no cases have been described although, theoretically, they are to be expected because of similar climatic conditions.

Synonymous Terminology

In the literature there has been a great variety of names used synonymously, e.g., Biundulant meningoencephalitis, Biundulant milk fever, Far Eastern forestencephalitis, Kumlinge-disease, Central European encephalitis (CEE), Russian spring-summer encephalitis, Tajga-encephalitis, Tick-borne encephalitis and Louping-ill. Certain differences exist clinically as well as in regard to the biological vector and antigen type.[17] It is of practical importance to distinguish between an eastern (Russian spring-summer encephalitis) and a western (Central European encephalitis) type.[4] The eastern type with Ixodes persulcatus as biological vector manifests itself clinically usually in one phase, and has a higher mortality than the Ixodes ricinus-transmitted diphasic western form.

Also on other continents tick-borne viral infections in man have become known, e.g., in India by Kayasanur forest disease, in Malaya the Langat (T.P. 21), in Japan the Japanese encephalitis, in North America the Powassan and Colorado tick fever, in Australia the Murray-valley encephalitis, and in Africa the Nairobi sheep disease[7,14,17,27,28]. These diseases certainly are more widespread than now suspected on the basis of serological examinations.

The Virus Host

The virus of Central European encephalitis can survive in several generations of the tick Ixodes ricinus. It is transmitted by tick bite to wild animals who develop a viremia but only rarely an encephalitis. Further spread occurs when the infected animal is bitten by susceptible ticks. Tick larvae feed on mice, the nymphs partly on small mammals, and the mature ticks almost always on large animals and sometimes man. The mouse-larva-nymph-mouse cycle represents a kind of virus reservoir. As the virus passes during viremia into the milk of infected animals, during the phase of viremia, infection is possible by drinking unboiled milk. Rarely do laboratory infections result from inhalation.[4,11,17,29]

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See editorial page 85.

Central European encephalitis shows a clear incidence with a peak in June and July.

The Carrier

Vector* herds exist in wooded areas.[5,19,21,24,29] Therefore farmers, woodsmen and hunters are especially exposed to infection. The variability of annual incidence through the years depends upon changes in vector concentration and the contamination rate. The combination of short winters and moist summers is said to cause an increase in tick population, resulting in an increase in infections.[22]

The Inoculation

At the site of the *tick bite* there is a localized inflammatory reaction and infiltration resulting from the local reaction to toxins.

The Incubation Period

In the *incubation period* (three to 21 days, usually 10 to 12) the already reproducing virus spreads from the lymph channels into the blood. In milk infection the virus is taken up by the epithelial cells lining the upper part of the alimentary tract, and the multiplying virus penetrates via the lymph vessels into the blood.

Inhalation Infection

In the rare case of inhalation infection, the virus would be transmitted from the olfactory epithelium and nerve fibers directly to the ganglions and central nervous system; in this case the so-called first phase of the illness would not exist. The vast majority of infections are abortive and inapparent.

The Stage of Viremia

After the incubation period, in the *stage of viremia (first phase,* average length four to six days) the clinically well-known general symptoms of viral infection appear: fever, mild upper respiratory manifestations and headache. Sometimes the illness ends in this first phase.

Organ Manifestations

Autonomic Nervous System

In other cases, a few days after viremia, the second phase with the *organ manifestations* of this pantropic virus follows. The quite variable symptomatology depends, among other things, upon the site of entry, the amount and virulence of the virus, and the general condition of the macroorganism. Gastrointestinal symptoms, disturbance of sweating, salivation and sphincter control are signs of involvement of the autonomic nervous system.

Central Nervous System

Infection of the central nervous system results in different manifestations, especially in meningitis, encephalitis, polioencephalitis and rarely radicular syndromes, as well as combinations of the above. In the spinal fluid protein content is slightly raised; occasionally pathological colloidal curves and a pleocytosis of several 100/3 cells p.cc are seen. These changes usually disappear after three to four weeks. The blood findings are characteristic of viral infection. The mortality varies considerably and may amount to several percent. There are no characteristic pathological anatomical findings. The differential diagnosis includes other viral infections, e.g., ECHO; Coxsackie-, parotitis-, herpes- and poliomyelitis virus.[4,16,17,24,30,31]

Diagnosis

Isolation of Virus

A definite diagnosis is only possible by means of isolation of the virus or serological examination. Except in some rare cases the isolation of the virus from blood is successful only in the first phase of infection and later from parenchymal cells of the central nervous system. However, isolation of the virus in the early, uncharacteristic stage of the illness is seldom attempted. Virus isolation from spinal fluid has been reported in isolated cases. In clinical medicine the serological methods are practically the only promising ones.[4,11,12,16,17,25,26,28] Three blood samples are recommended. The first is to be taken at the earliest sign of neurological involvement, the second after two weeks, the third four weeks after the first sample.

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*See Test Your Word Score Page 89.

Serological Studies

Unfortunately serological studies of Central European encephalitis are made in only a few centers of Western Europe. A combination of three serological methods has proven to be most useful: the hemagglutination inhibition test (HIT), the complement fixation test (CFT), and the neutralization test (NT). The goal of all three reactions is to detect specific antibodies. With the hemagglutination test common antibodies against other strains of ARBOR-B-virus are detected; however, with the homologous antigen higher antibody titers are found. Therefore the hemugglutination test is not type-specific; this also applies to the complement fixation test. The complement fixation test is suitable only in detecting fresh cases, because complement-fixing antibodies appear about three weeks after the beginning of neurological involvement; six months later they are no longer detectable by a dilution of 1:4. According to the literature the complement fixation test is positive in only two thirds of the cases with a positive neutralization test.

The neutralization test is the most specific. Since it is type-specific it is not unimportant which strain is used in the neutralization test in a given case. Often there is no isolation strain from the geographical area of infection available for serological purposes. For this reason generally the Czechoslovakian strain "Hypr" is used. But this may lead to false-negative results. Neutralizing antibodies in man are always present at the beginning of the second phase of illness. Practically, therefore, a negative neutralization test (less than 1:5) at the beginning of the second phase eliminates Central European encephalitis as the cause of infection. However, a positive neutralization test (1:40) does not tell us how old the infection and antibodies are.

The titer change is decisive (comparison with earlier or later antibody titers). A rise in titer is frequently found if the first examination was made early in the infection; the titer maximum is reached at the end of the first month of central nervous system involvement. Neutralizing antibodies probably are found in man years after infection. A positive titer in dilution of 1:5 at the beginning of neurological involvement indicates an old infection with Central European encephalitis virus, whereas a titer of 1:40 makes an acute infection probable. A rise in titer in the neutralization test and in the hemagglutination test, as well as a positive complement fixation test, is proof of recent infection.[4,5,11,12,16,17,19,20,27,29]

Treatment

The problem of *active immunization* through vaccination against Central European encephalitis-virus is not yet satisfactorily solved. Preventive methods such as suitable clothing for woodsmen, boiling of milk (especially goats' milk), reducing tick population, vaccination of farm animals, and perhaps reconvalescent serum are of value. There is no specific *therapy*. Gamma globulin has only a prophylactic value because at the earliest possible moment of diagnosis of Central European encephalitis, antibodies are already present in serum and a further application of antibodies cannot improve the prognosis.

Personal Observations

The frequency of viral disease of the central nervous system of unknown origin in the summer months and stimulation of interest resulting from investigations in West Germany[1,19,24,25,26,29] have led us to search more carefully for cases of Central European encephalitis in Switzerland. As systematic serological examination of large groups of patients was technically impossible, we depended primarily upon a history of certain or questionable tick bite. Serological examinations were not made in all cases and in some only after many months. A local virus strain is not available for serological purposes; hence a type-specific neutralization test could not be made.

TABLE I

Case Nr., Age, Profession	Case and History of tick bite	Clinical features and Seasonal incidence	Cerebrospinal fluid	Serological tests	Late findings
1. Paul K. 45 years Manager	+ +, several, mostly in spring 1964	Chronic meningitis lasting months August 1964	Nov. 1965: 41/3 cells per cc, 48 mg % Protein (Kafka method)	Dec. 1966 HIT: Strain "Hypr" 1:40, Fränk. virus— CFT— NT (mice and tissue culture)—	Complete recovery
2. Walter R. 59 years Instructor	Palm-sized bluish reddening on the inside of the right thigh	Diabetes mellitus, meningoradiculitis August 1964	128/3 cells per cc. normal protein content	Sept. 1966 HIT and CFT— (Strain "Hypr") Fränk. virus: 1:40/1:20 pos. 3 months later questionable pos. CFT—, NT—	In October 1966 almost complete recovery
3. Werner A. 41 years Salesman Gamewarden (See text)	+ +, 22, 8, 65, with local reaction	Severe meningoencephaloradiculitis End of August 1965	1500/3 cells per cc., 103 mg% protein	7.9.1965 HIT above 1:20 pos CFT above 1:128 pos NT (May 1967) 1.256 pos Neutralisationsindex 4,00 CFT 1:4	Moderately severe asymmetrical motor deficit 2 years after infection
4. Franz M. 50 years Physician	Painful redness in the right axilla	Meningitis with facial palsy of the peripheral type on both sides August 1965	600/3 cells per cc., 144 mg% protein "paretic" Zone I curve in the mastix reaction	....	Complete recovery
5. Martha B. 57 years Housewife	Nov. 1966 questionable in the neck region	Meningoencephaloradiculitis End of November 1966	Dec. 1966 152/3 cells per cc., 30 mg% protein	HIT: "Hypr" 1:10 F.V. 1:40 (Febr. 67 1:10) CFT and NT—	Moderately severe sequelae in February 1967
6. Albert D. 69 years Businessman	Questionable on the left costal margin; local reactions spreading to the neck and abdomen	Severe meningoencephaloradiculitis Beginning of June 1966	Oct. 1966 169/3 cells per cc., 60 mg% protein Zone I "paretic" curve in the mastix reaction	October 1966 HIT: "Hypr" 1:10/1:20 CFT: 1:8/1:8 F.V.:— NT—	Slight paresis of the small handmuscles August 1967
7. Fred S. 33 years Teacher	Local redness and infiltration on the right forearm (in the military service)	Brachialgia July 1966	....	....	Unknown
8 Amande T. 62 years Housewife	+, local reaction on the left side of the thorax	Facial palsy of the peripheral type on the right side July 1965	....	January 1967 HIT: "Hypr" 1:10 F.V. 1:20 CFT— NT—	Residual neurological defect
9. Romano S. 20 years Tailor	Illness during military service	Chronic meningoencephaloradiculitis September 1964	September 1964 90/3 cells per cc., normal protein path. colloidal curve. April 1966 62/3 cells per cc., normal protein March 1967 58/3 cells per cc., normal protein	July/August 1966 HIT: "Hypr" 1:160 CFT 1:4 August 1966 HIT: 1:320 CFT 1:16 F.V.— March 1967 HIT: 1:10 CFT 1:8	Mild sequelae

We have observed *nine suspected cases*. They are summarized in Table 1. An instructive case follows in detail (Case 3 in Table 1).

Case Report

A. Werner*, male, aged 41, salesman and voluntary gamewarden of forest direction in Berne. In the months before illness several tick bites, the last on August 22, 1965, on which evening he found a pea-sized tick in the right inguinal region. In the following days redness, swelling and slight infection developed at the site of the bite. On August 29 malaise and the feeling of fever; on the following day a fever of 38.5°C, headache, and increasing pain in the right inguinal region; on August 31 neck stiffness, slight paralysis of the arms; on September 1 difficulty in swallowing and diplopia. A spinal tap showed elevated protein (103 mg %) and 1500/3 cells per cubic millimeter. An increase in flaccid paralysis followed. On September 6 somnolent, lethargic, flaccid paralysis of all extremities, especially proximal on the arms which could no longer be raised actively. Dyspnea and weakness of cough. Babinski positive on both sides. Serological findings on September 9, hemagglutination test for Central European encephalitis greater than 1:20 positive, complement fixation test more than 1:128 positive. Slight simultaneous agglutination of adenovirus, mumps and Coxsackie B2.

During the next weeks recovery was slow, with some residual paralysis. Intensive physical treatment followed. A control examination in May 1967 showed generalized, moderate, flaccid paralysis of the right arm, especially proximal, with obvious muscle atrophy. Slight weakness and atrophy of the left deltoid muscle. Stretch reflexes lively and symmetrical, no sensory disturbances. Light to moderate paresis, especially distal, of the right leg. Babinski inconstantly positive on the left side. Dysesthesia on the lateral side of the right thigh. Serological findings on May 9, 1967: complement fixation test 1:4 positive, neutralization test 1:256 positive (tested with 1000 ID50). Neutralization index 4.00†

Epicrisis: serologically proven Central European encephalitis occurring after tick bite with the clinical picture of serious meningo-encephaloradiculitis. Recovery with residual asymmetrical motor damage.

Discussion

As shown in Table 1 we were successful in just one case in obtaining serological proof of tick-transmitted infection of the virus of Central European encephalitis. It proves, however, that the virus of Central European encephalitis is present in Switzerland and that increasing numbers of infections are to be expected. The other cases were suspect, partly because of clinical evidence and partly because of the serological finding of a previous contact with the virus of Central European encephalitis, although it could be proved that this contact was responsible for the present illness. In two cases no serological examinations were done; in four others the first examination took place four to 28 months later, so that no significant changes in titer could be expected. We cannot judge the value of a negative neutralization test for the strain "Hypr" or fränkisches virus" in eliminating Central European encephalitis after such a length of time. It would be important to conduct examinations with a virus strain isolated from our own immediate geographical area.

In suspected cases, early and repeated serological examinations (three times at intervals of two weeks) should be made. This was not possible in all of our cases, as many were referred late in the course of infection. A history of tick bite was proven in three cases by detection of the insect. Twice typical local inflammatory changes were also found. In five other cases local changes suspicious of possible tick bites were found in addition, when exposure in a wooded area had taken place. In only one case, that of a soldier in military service, was there no history in this respect, although as a soldier he was potentially exposed to tick bites.

The age of the patients at the time of infection varied between 20 and 69 years. Seven males and two females were affected. The seasonal incidence with eight cases in the months of July to September (one case in November) correlates with the distribution reported in cases of Central European encephalitis. The clinical manifestations appeared four times as meningoencephaloradiculitis, twice as meningitis, once as meningoradiculitis, once as a peripheral facial paralysis, and once as a brachialgia. The blood picture corresponded to the findings in viral infection; and in cerebrospinal fluid a pleocytosis between 40/3 and 1500/3 cells per cubic millimeter, a protein concentration ranging from normal to 144 mg% (Kafka method), and sometimes a pathological colloidal curve were found. Pathological spinal fluid findings were present for months to more than two years after illness. As a result the course of illness was sometimes very much prolonged. Follow-up studies revealed complete recovery in three cases and residual neurological damage of varying degrees in five others. One case could not be followed.

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*The patient was first seen in the Clinic of Internal Medicine of the Tiefenau Hospital. We wish to thank Prof. G. Riva for permission to publish this case.

†Professor Ackermann of the Neurological Clinic of Köln (Western Germany) was kind enough to do the serological tests.

Summary

One serologically-confirmed, and eight clinically suspected cases of Central European encephalitis transmitted by tick bite and occurring in Switzerland are reported. This ARBOR-virus infection is steadily spreading toward Western Europe and is clinically manifest at the outset as a mild upper respiratory infection, later showing organ manifestations, and may culminate in more serious symptoms of meningitis, encephalitis, polioencephalitis radiculitis or a combination of these. The modes of infection, the seasonal and geographical incidence, as well as the clinical and serological diagnosis are discussed.

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22-32. May be secured from the author.

He looked at me as if I was a side dish he hadn't ordered.—Ring Lardner

Old men are fond of giving good advice to console themselves for their inability to give bad examples.—Francois de La Rochefoucauld

Ferrokinetics in Polycythemia and Iron Deficiency Anemia*

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THE CLOSE RELATION between plasma iron turnover and erythropoietic activity has been clearly demonstrated in the normal and in many pathological conditions with increased or decreased red cell production.[1,5,6] Therefore it may be assumed that the maintenance of an elevated total red cell volume in polycythemia is associated with an increase of plasma iron turnover. While in most cases of secondary polycythemia one can observe a close parallelism between total red cell mass and ferrokinetic, polycythemia vera is most often characterized by a disproportionate elevation of plasma iron turnover.[5,7,9,15] Ellis and coworkers[2] observed recently that untreated polycythemia vera is regularly associated with depleted marrow iron stores in contrast to the normal or increased amount of iron seen in cases of secondary polycythemia, and they demonstrated that plasma iron disappearance time is highly affected by depletion or repletion of iron stores in both primary and secondary polycythemia.[3] They concluded that differences in iron kinetics‡ between the two diseases are more related to the size of available iron stores than to the type of polycythemia.

In a simultaneous study we reached the same conclusions based upon the observation that iron deficiency anemia is characterized by a ferrokinetic pattern similar to that of primary polycythemia.[14]

It is the purpose of this paper to re-examine the clinical value of ferrokinetic studies in polycythemia.

Material and Methods

Thirty-six patients were investigated: seventeen with polycythemia vera (sixteen untreated, one treated), nine with polycythemia secondary to decreased oxygen saturation in connection with chronic respiratory insufficiency or cardiac malformation, six with rela-

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*This work was supported by a grant of the Swiss National Foundation for Scientific Research.

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‡See Test Your Word Score Page 89.

tive polycythemia, and five with anemia secondary to iron deficiency. The exact diagnosis was made in each case on the basis of clinical, laboratory and cytological data.

Hematological routine examinations were done by standard techniques of the Inselspital Berne. Erythrocytes and leucocytes were counted in an electronic counter (Coulter Counter, model A). Platelet counts were made, using phase microscopy. Alkaline phosphatase activity in granulocytes was determined by the method of Merker and Heilmeyer.[10] Serum iron was determined by the method of Lauber.[8] Bone marrow smears were stained for iron, using the Prussian Blue reaction. Measurement of total red cell volume was done with chromium-51 labeled red cells by the method of Hughes Jones et al.[11] Plasma volume was calculated from the total red cell volume with the whole body hematocrit (venous hematocrit x 0.87). Plasma iron disappearance was measured after in-vitro labeling of patient plasma with 4-8 microC ^{59}Fe; plasma iron disappearance time, serum iron concentrations and plasma volume by the formula of Huff and coworkers[5] P.I.T. =

$$\frac{0.693 \cdot \text{Plasma volume (ml)} \cdot \text{Pl.Fe.(mg/1)} \cdot 24}{T\frac{1}{2}\ \text{(minutes)}}$$

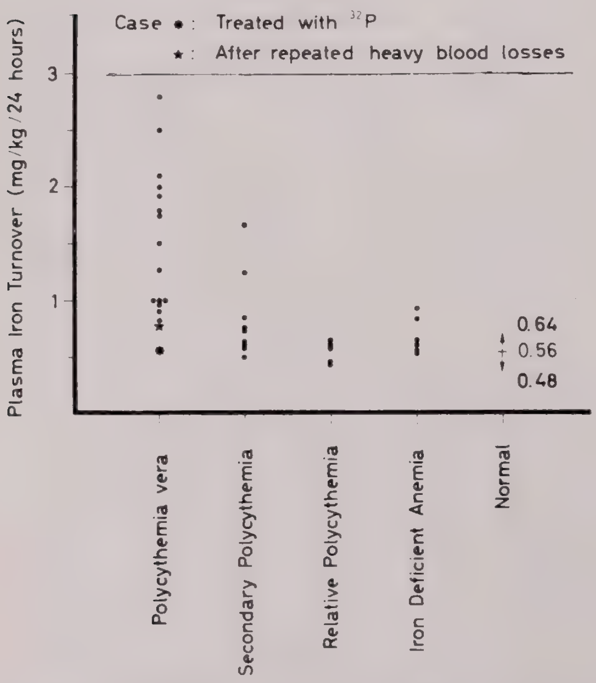


Fig. 1—Plasma iron turnover in different types of polycythemia and in iron deficient anemia.

The results of total red cell volume were expressed in ml/kg body weight, those of plasma iron turnover in mg/kg body weight. In obese patients the actual weight was replaced by the theoretical weight, calculated from the height by the formula:
theoretical weight (kg) = height (cm) − 100.

Results

Results of blood volume determinations, serum iron concentration and studies of iron metabolism are presented in the Table and Figure 1. The mean total red cell mass and plasma volume are slightly higher in polycythemia vera than in secondary polycythemia, but the wide scattering of the individual figures in both groups makes any diagnostic evaluation elusive in the individual case.

Discussion

Plasma iron kinetics are normal in all patients with relative polycythemia. This was to be expected since relative polycythemia is due to faulty regulation of plasma volume and not to a disorder of erythropoiesis. In secondary polycythemia, plasma iron turnover was found to be moderately increased, whereas it was greatly elevated in the majority of the patients with untreated polycythemia vera. This represents a further confirmation of the findings of Huff and other investigators.[5,7,9,15] However, several observations in our material warrant more detailed comment.

Iron Turnover

Plasma iron turnover values between 0.8 and 1.0 mg/kg/day are frequently encountered in secondary as well as in primary untreated polycythemia. This overlap restricts the diagnostic value of the method.

In a few instances secondary polycythemia may be associated with a very high increase in plasma iron turnover.

Case B.F., 35-year-old male, height 182 cm, weight 135 kg. This obese patient was suffering from severe chronic bronchitis complicated by a Pickwick syndrome with a resulting arterial oxygen saturation of less than 70%. The total red cell volume reached 6000 ml within a few years. There was no clinical suspicion of concomitant polycythemia vera.

The clinical situation of this patient was therefore characterized by the extraordinary degree of polycythemia and the relatively rapid development of the disease.

Normalization of Blood

Effective cytostatic treatment of polycythemia vera with 32 P or chemotherapeutic agents is followed by a rapid *normalization of plasma iron turnover*, the latter thus providing a useful tool for early judgment of the effectiveness of the therapeutic procedure. This normalization of plasma iron kinetics occurs within a few days after injection of 32 P, whereas an appreciable lowering of the total red cell mass—consequent on the long erythrocyte life span—will not occur before four to six weeks.

Heavy blood loss with consecutive *normalization of blood volume and hematocrit* does not lower plasma iron turnover to the same extent. This may be of great diagnostic importance when a history of important blood loss is opposed to a normal hematocrit as in the following case.

Case K.G., 57-year-old female. This patient entered the hospital with a history of intestinal blood loss which was not in accordance with a hematocrit of 42%. Plasma iron turnover at that time was still elevated to 0.8 mg/kg/day and pointed to the diagnosis of polycythemia vera in a patient with heavy blood loss.

Erythropoietic Activity

The ultimate proof of a disproportion between plasma iron turnover and erythropoietic activity in polycythemia vera presumes the direct measurement of erythropoiesis. This is not possible at the present time; however, one can evaluate erythropoietic activity by measuring total red cell mass and the rate of both intra- and extramedullar hemolysis.

In our patients we have done no erythrocyte survival studies and no measurements of bile pigment excretion. Several investigators have demonstrated normal red cell survival in polycythemia vera at least in the early stages of the disease when the splenomegaly is not yet pronounced and no extramedullary erythropoiesis is present.[4] Likewise in that stage of the disease morphological criteria which might presume an enhanced intramedullary hemolysis do not exist. Our patients were examined soon after diagnosis had been established, and they presented no signs of increased peripheral or medullary hemolysis as judged by reticulocyte counts and bone marrow morphology. It seems therefore reasonable to consider total red cell mass in our patients with polycythemia as an acceptable parameter for erythropoietic activity.

TABLE
Blood Volumina, Serum Iron and Ferrokinetic Datas
(mean and range)

	Number of cases	PCV	Total red cell volume (ml/kg)	Plasma volume (ml/kg)	Serum iron (γ/100 ml)	Plasma iron disappearance time (T_{50} in min.)	Plasma in turnover (mg/kg/da)
Polycythemia vera							
— untreated	15	60.1 (45-71)	57 (43.2-73)	47.4 (35-60)	56.5 (20-91)	16.9 (6-43.5)	1.62 (0.82-2.8)
— treated (^{92}P + phlebotomy)	1	41	25	46	20	20	0.57
— after heavy gastro-intestinal bleeding	1	44	23.4	35	23	10	0.8
Secondary polycythemia	9	60.9 (55-67)	49 (34.3-81)	42.7 (35.5-53.5)	102.8 (20-179)	60 (8-107.5)	0.83 (0.5-1.67)
Relative polycythemia (Polycythemia of stress)	6	54.3 (50-59)	32 (26-36.9)	33 (28-36)	116.5 (72-186)	77.17 (54-105)	0.55 (0.44-0.64)
Iron deficiency anemia	5	33.6 (20-42)	19.8 (13.5-25 5)	54 (4.45-63)	27.4 (12-47)	22 (11-38)	0.63 (0.53-0.83)
Normal mean ± one standard deviation	20	45±4	29±3	43±4	110±25	78±18	0.56±0.08

The disproportionate rise of plasma iron turnover indicates that a lesser part of iron leaving the plasmatic pool is used for erythropoiesis than in the normal individual: a situation well known in idiopathic hemochromatosis where an increased exchange takes place between plasma iron and storage iron. A similar situation of relatively increased plasma iron turnover is observed in iron deficiency anemia as demonstrated in Figure 2. An explanation for this peculiar fact has been offered by Pollycove[13] and Najean and coworkers,[12] who presented evidence that iron on its way from plasma into the erythrocyte precursor passes through a labile iron pool. Its size and exchange rates have been evaluated by mathematical analysis of the plasma iron disappearance curve. In the presence of iron deficiency this pool was found to be small, but its rate of exchange with the plasma iron pool very high. Iron is then shifting rapidly from plasma in this labile pool and in part back to plasma, resulting in an increased plasma iron turnover as compared to circulating red cell mass. It has been postulated that this labile iron pool might be located on the cell surface of the erythrocyte precursors[13] and possibly even in part attached to circulating reticulocytes; others believe that this exchangeable compartment is diffuse in the whole organism (marrow, liver, spleen, intestine).[12]

Iron Turnover vs. Red Cell Mass

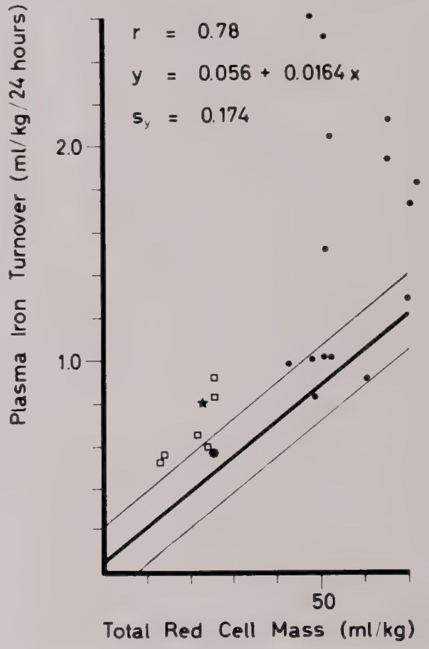
Figure 2 demonstrates the linear relationship between plasma iron turnover and total red cell mass for normal individuals and for patients with relative and secondary polycythemia, whereas many cases with polycythemia vera present a disproportionate increase of plasma iron turnover similar to patients with iron deficiency. It seems tempting to speculate that the observed abnormality of plasma iron turnover in polycythemia vera is in fact a mere consequence of a state of iron deficiency and not inherent in the nature of the disease.

Few investigators have drawn attention to the frequency of the obvious iron deficiency in patients with untreated polycythemia vera. As shown in Figure 1 serum iron levels were low in all of our patients. Moreover, in agreement with Ellis and coworkers[2] we could detect no stainable iron in the bone marrow of five patients examined. The frequency of iron deficiency in polycythemia vera is not surprising; in the normal individual approximately two thirds of the total body iron are located in the circulating erythrocytes. An increase of this red cell mass by only fifty percent would therefore shift all the storage iron of the body into the red cells.

Actually it is more surprising that patients with secondary polycythemia, who do have a similar increase in total red cell mass, present no signs of iron deficiency. One may speculate that the duration of the disease is important.

Conclusion

Development of secondary polycythemia in patients with chronic respiratory or cardiac disease is usually very slow and often starts in early childhood. This gives the organism a fair chance to compensate the increased iron "sequestration" in the circulating red cell mass by increased absorption from the gut. Although



Note: Polycythemia vera • ● ★
Iron Deficiency □

The regression line was calculated from a group of 25 individuals (10 normals, 6 relative polycythemia, 9 secondary polycythemia)

Case ● : Treated with ^{32}P
★ : After repeated heavy blood losses

Fig. 2—Relation between plasma iron turnover and total red cell mass in patients with polycythemia vera and iron deficient anemia.

no pertinent data are available it seems very likely that the time interval between onset and full clinical manifestation of polycythemia vera is usually not more than a few months, much too short a period to allow effective compensation of the "iron loss" by increased absorption.

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New Look to Medicine

The years passed and the frontier was changing. Even Dr. Weideman's San Antonio was becoming educated not only to scientific ways but to scientific jargon. In 1882 a ranch-country scribe summed up what he felt about the new look to medicine in the city of the Alamo. In his home town people still died of simple frontier diseases such as lead poisoning, but in San Antonio, well now! Science was running rampant.

"Over in San Antonio," he observed, "the people die of icterus senilis, of seven kinds of tuberculoses, of icterus amenorrhoea, intestinal pulmonalis, and five other kinds of icterus. They can also die, if they want to, of anenisina, colica flatulenta biliosa—particularly when complicated with atropia medullae spinalis or morasmus infantium caused by too much vox populi, nux vomica, e pluribus unum, particularly etc."*

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*Richard Dunlop: Doctors of the American Frontier.

Art of Living

The art of living is more like that of wrestling than of dancing; the main thing is to stand firm and be ready for an unforeseen attack.—Marcus Aurelius

It's spring when you turn on the heat that yesterday you thought you'd turned off for the year.—Changing Times

Nobel Prize Winners In Medicine and Physiology

Emil Theodor Kocher 1909

For his work on the physiology, pathology, and surgery of the thyroid gland

"In the spring of 1883, at the Congress of the German Surgical Society (Gesellschaft fur Chirurgie), we announced that some thirty of our first one hundred thyroidectomies, which we could follow up and investigate, presented a quite definite, characteristic disease-picture, which we designated simply with the name cachexia strumipriva. This appeared in its completely distinct form only in those patients from whom we had removed the whole thyroid gland; with no more than transitory signs, on the other hand, where all goiter tissue had supposedly been removed, but where in point of fact a piece had remained behind, which grew larger.

"Isolated observations on the connection of cretinoid disturbances with changes in the thyroid gland had already been made by early investigators.

"At the time (April 1883) when, in Berlin, I described cachexia strumipriva as the *constant* result of total excision, on the ground of numerous observations, and warned against such excision because it always leads to consequences displaying a well-marked cretinoid character, a brilliant discourse was delivered at the same congress by a first-rate surgeon on the advantages and technique of total excision.

"Further corroborative information on the nature and conduct of the new disease soon followed my contribution . . . At a famous meeting of the Clinical Society in London (November 23, 1883) Felix Semon referred to my work and mentioned a confirmatory case, following total excision by Lister; and Ord read a letter I had written to him on the etiology of the disease and the connection of myxedema with cachexia thyreopriva.

"The impulse was thereby given for the splendid investigations of the Clinical Society Committee, which came to the conclusion that myxedema and sporadic cretinism are identical, and probably cachexia strumipriva also, and that close connections exist with endemic cretinism."*

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*Emil Kocher as quoted in Theodore Sourkes: Nobel Prize Winners in Medicine and Physiology, 1966.

Emil Theodor Kocher, M.D.

Emil Theodor Kocher, eminent Swiss surgeon, was born in Berne in 1841. He studied there and at Berlin, London, Paris, and Vienna, where he was one of Albert Billroth's pupils. Later he returned to his native Berne to become Professor of Surgery there and subsequently Director of the Surgical Clinic, a post he held for 45 years.

Most notable of his achievements was his application of experimental and physiological principles to surgery of the thyroid gland; for that contribution he received the Nobel Prize in Medicine and Physiology in 1909.

By 1912 Kocher had to his credit 5,000 operations for goiter. While thyroid gland surgery was his specialty, recognition was also accorded him for meritorious and pioneer work in other fields: reduction of shoulder dislocations, in particular, and modifications of older methods of surgery on the stomach, lungs, gallbladder, tongue, and cranial nerves, and also for hernia.

When Kocher died in 1917 the British Medical Journal said: "The world loses its greatest surgeon."

Fatal Posttransfusional Hepatitis in Switzerland

K. STAMPFLI, M.D.*
Berne, Switzerland

In June 1965 the Committee on Plasma and Plasma Substitutes of the National Academy of Sciences and the National Research Council published a study on the incidence, mortality and prophylaxis of posttransfusion hepatitis in the United States.[1] This board of experts concluded that in the United States, an average of five cases of manifest posttransfusion hepatitis occurs for every 1,000 transfusions administered. Referring to the papers of Allen[2] and Grady[3] they estimated that 10 to 12% of such cases terminate fatally. Supposing that some six million whole blood transfusions are administered each year to about 1.8 million patients, they calculated that 30,000 cases of posttransfusion hepatitis must be expected annually in the United States, of which some 3,600 would be lethal. These figures were impressive and called for an assessment of the problem in our country, too.

Results of Survey

We studied the autopsy records of the University Departments of Pathology from Basel, Berne and Zürich for the years 1960 to 1964 inclusive. Deaths due to hepatic failure were screened out and subjected to retrospective evaluation. All cases in which the pathologists found evidence of "hepatitis," "jaundice" or "liver dystrophy" were included.

In the departments mentioned, a total of 25,730 autopsies were performed during the five-year period 1960 through 1964; 532 cases, or 2.1%, were considered to have died from hepatic failure. From the clinical history and the complete pathological findings it was possible to divide these 532 cases into the subgroups summarized in Table 1.

Discussion

The statistical analysis of these results and the study of the individual case histories published in detail elsewhere[28] yield the following picture:

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* Department of Pathology, Universities of Basel, Berne and Zürich, and Central Laboratory of the Swiss Red Cross Blood Transfusion Service, Berne, Switzerland.

Statistical Significance

The average incidence of fatal posttransfusion hepatitis in the autopsy material of the three departments participating in the study was 0.12%. Assuming a Poisson distribution* to be valid, we obtain a 95% confidence interval of 0.08-0.16%. In this calculation, all cases in which a connection with the transfusions administered remained a possibility only are included. The regional differences—0.14% in Basel, 0.12% in Berne and 0.10% in Zürich — are irrelevant. The statistical evaluation of these figures by means of the Chi-square test reveals no differences of the 5% level.

It is hardly justified to accept these results as being generally valid for Switzerland without further scrutiny. It may reasonably be supposed that hepatic failure is more frequent among deaths coming to autopsy than among deaths not subjected to post-mortem examination. Also, the proportion of autopsies relative to fatal deaths shows considerable regional differences. Whereas only 7.6% of all registered deaths in the Berne area came to autopsy in the period under study, the percentages in Zürich and Basel were 27 and 52, respectively. During 1960-1964, a total of 58,434 autopsies were performed in the department of pathology and forensic medicine throughout Switzerland, equalling 22% of the 268,821 deaths registered in the country during the same period. If we apply the mean mortality rate of 0.12% calculated as previously stated to the total number of autopsies performed in Switzerland during 1960-64, we may estimate it to have included some 70 cases of posttransfusion hepatitis, or an average of 14 cases a year. If, furthermore, we base our assessment on an upper limit to the mortality figures on the assumption that the incidence of posttransfusion hepatitis was equally high among autopsied and non-autopsied deaths, we arrive at an estimated 320 deaths from posttransfusion hepatitis in Switzerland during the five-year period 1960-64. During the same period the Swiss Red Cross Blood Transfusion Service delivered 702,436 units of whole blood to hospitals and physicians throughout Switzerland. Simultaneously, 91,734 donations of fresh whole blood were arranged for. The Central Laboratory provided 94,053 units of single-donor dried plasma and 15,293 units of two-donor fraction I preparation (fibrinogen, antihemophilic globulin). As judged from the total of these figures, the risk of contracting a fatal posttransfusion hepatitis amounts to between 1:2800 and 1:12.900 per unit administered. Supposing — as did the American Committee — that the average patient receives three units of whole blood or blood products, the mortality risk per treatment lies between 1:900 and 1:4300.

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*See Test Your Word Score Page 89.

TABLE I

Among 532 cases of fatal hepatic failure, we find 74 cases of viral hepatitis without any history of blood transfusion, 21 cases of probable posttransfusion hepatitis and a further 10 cases in which that complication was considered possible.

Hepatic failure with cirrhosis or dystrophy, due to:		
—chronic alcoholism	208	(39.1%)
—further toxic agents	22	(4.1%)
Hepatic failure with occlusive jaundice, due to:		
—biliary tract inflammation	52	(9.8%)
—malignancy	101	(19.0%)
—echinococcus alveolaris	4	(0.7%)
Hepatic failure with inflammation, due to:		
—Weil's disease	2	(0.4%)
—epidemic viral hepatitis	74	(13.9%)
—posttransfusion hepatitis	31	(5.8%)
Hepatic failure with cirrhosis or dystrophy of unknown origin	38	(7.2%)
	532	(100.0%)

Incidence of Fatal Posttransfusion Hepatitis

As a check on the validity of these calculations, we may base our estimate of the incidence of fatal posttransfusion hepatitis on the findings pertaining to the town of Basel, in which 6,232 of 11,953 deaths, or 52% were autopsied. An estimate of the minimum incidence is obtained as follows: Assuming no deaths from posttransfusion hepatitis to have occurred in the group not examined post mortem and including only "probable" cases, we have 10 cases out of 11,953 deaths, or a mortality of 0.08%. The maximum incidence may be estimated by assuming the incidence of posttransfusion hepatitis to have been equally high in the autopsied and non-autopsied groups and including the "possible" cases too. This yields 25 cases out of 11,953 deaths, or a mortality rate of 0.21%. Now a total of 88,367 units (83,093 of whole blood, 3,501 of dried plasma and 1,773 of fraction I preparations) were provided by the regional blood banks during the period under study. In other words, the risk of contracting a fatal posttransfusion hepatitis was between 1:3500 and 1:8500 per unit of blood and blood products. If we assume again that the average patient received three units, the mortality risk per treatment lies between 1:1200 and 1:2800. As will be recalled, the corresponding estimate obtained by extrapolation of the results from all three cities to the whole Country were 1:900 and 1:4300.

For the reasons specified, the data from the town of Basel are probably more precise. If they are extrapolated to yield a nation-wide estimate, the following results are obtained: In Switzerland 268,821 deaths were recorded from 1960-1964. A mortality rate from posttransfusion hepatitis of 0.08-0.21% thus equals between 43 and 113 deaths annually. Let us compare this estimate to that arrived at by the American Committee: During 1960-1964, a total of 8,786,000 deaths were recorded in the United States, or 32 times the figure for Switzerland. If the data obtained for Basel are extrapolated to the United States, we arrive at between 1,400 and 3,600 annual deaths from posttransfusion hepatitis. The United States estimate was 3,600 deaths a year, which agrees remarkably well with the upper mortality limit calculated for Switzerland.

As previously mentioned, we estimated the mortality risk per unit of whole blood or the blood products specified to lie between 1:3500 and 1:8500, as judged from the data obtained for the town of Basel. According to Gsell[4] a lethality rate of 10 to 12% would be too high; so we may postulate the lethality to equal 5% for the calculation to follow. With a mean mortality risk of 1:5000, we may estimate that one case of clinically manifest posttransfusion hepatitis will occur for each 250 units administered. This figure agrees with the American rate estimated to be 1:200 and also with the morbidity figure of 0.2 to 0.5% per transfusion previously arrived at for Switzerland by Hässig[5] and Dubs.[6]

Relation to Preexisting Disease

From the study of the individual case histories published in detail elsewhere,[28] the impression emerges that fatal posttransfusion hepatitis frequently occurs as a complication

TABLE 2

Autopsies—Deaths—Transfusions—Hepatitis

	Berne	Basel	Zurich
Autopsies performed 1960-1964:	3,377	10,181	12,172
Total number of deaths registered during the same period in the area served by this department	44,192	17,823	45,005
Total number of whole blood units released by the transfusion centers in the same period and area	125,807	92,943	133,926
Cases of posttransfusion hepatitis			
probable	2 } 4	11 } 15	8 } 12
possible	2	4	4

of severe preexisting disease. Elderly patients are especially prone to contract it. Among our 21 cases with "probable" posttransfusion hepatitis, only one was less than 45 years old; among the 10 cases of "possible" posttransfusion hepatitis, a single patient was younger than 57. Thirteen patients with "probable" posttransfusion hepatitis died from acute or subacute liver dystrophy; in another four, the pathological diagnosis was subacute or acute hepatitis. Two patients suffered from postnecrotic cirrhosis of the liver. For the 10 cases of "possible" posttransfusion hepatitis, liver dystrophy and hepatic cirrhosis were recorded in five patients each. Among the patients with "probable" posttransfusion hepatitis, six out of 21 suffered from malignant disease, four from complicating diabetes mellitus and two from toxic liver damage due to alcohol or carbon tetrachloride. Among the 10 patients with "possible" posttransfusion hepatitis, we encountered one case each of carcinoma and chronic lymphatic leukemia, two cases of hepatic damage due to chronic alcoholism and two cases possibly complicated by drug-induced liver damage. In five patients with "probable" posttransfusion hepatitis, dried plasma or fibrinogen must be considered as a source of infection besides whole blood; two out of 10 cases of "possible" posttransfusion hepatitis also belong to this category.

Our case records[28] are too few to permit final conclusions to be drawn as to the kind of preexisting disease especially susceptible to fatal posttransfusion hepatitis. However, they appear to confirm the impression recorded by other authors[2,7-11] that increasing age, preexisting liver damage or malignant disease increases the risk of a fatal course of posttransfusion hepatitis.

Additional information on the relationship between preexisting disease and the course of posttransfusion hepatitis may be obtained from a number of reports analyzing the case histories of patients with this complication.[5,6,7,12-27] The 19 papers studied by us contain 209 cases of posttransfusion hepatitis, 45 of which—or 21.5%—terminated fatally. Of the total number of patients, only 35 were less than 30 years old when afflicted with the sequelae of transfusion, the remaining 174 patients belonging to the higher age group. Among all patients, 54 suffered from preexisting gastrointestinal disease, 28 of these from an ulcer of the stomach or duodenum. Malignancy was present in 29 patients and 11 suffered from biliary or pancreatic disease. In nine patients, preexisting liver damage was recorded, due either to chronic alcoholism (two cases), previous epidemic viral hepatitits (two cases), or to morphine addiction, carbon tetrachloride poisoning, sequelae of hepatic coma or preeclampsia. Seventeeen female patients were pregnant or had suffered an abortion. Five cases were complicated by diabetes mellitus. We consider it remarkable that in patients with hematological disease such as leukemia or pancytopenia, requiring multiple transfusions, the risk of contracting posttransfusion hepatitis appears to be small. Among the 209 case histories found in the literature, there were only two instances of chronic leukemia.

Conclusions

From the study presented, we must conclude that the administration of a single unit of whole blood or dried plasma carries a mortality risk from posttransfusion hepatitis alone about equalling that of childbirth, or that of everyday surgical interventions such as herniotomy, tonsillectomy, or the removal of a non-perforated appendix. Despite the immense amount of labour devoted to the prevention of posttransfusion hepatitis, prophylactic methods of proven value are not yet available. For this reason, every transfusion of whole blood, dried plasma or fraction-I-preparations obliges the physician responsible for their administration to weigh the expected benefit carefully against the damage which such therapeutic measures may cause.

Among a total of 25,730 autopsies performed at the Departments of Pathology in Basel, Berne and Zürich in the five-year period 1960-1964, hepatic failure was the cause of death in 532 cases (2.1%). Within this group we found 74 cases of viral hepatitis without a history of blood transfusions, 21 cases of "probable" and 10 cases of "possible" posttransfusion hepatitis. From these figures a mean mortality rate of 0.12% for posttransfusion hepatitis may be deduced. On the basis of additional statistical data, collected mainly in Basel where more than 50% of all deaths came to autopsy, the mortality risk per treatment with an average of three units of blood was calculated to range from 1:1000 to 1:4000. From the evaluation of individual case histories it is concluded that in the majority of patients who succumbed to posttransfusion hepatitis, there was evidence of severe underlying disease, notably preexisting liver damage, gastrointestinal disease, or malignancy. This conclusion agrees with other reports in the literature.

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If this is coffee, please bring me some tea; but if this is tea, please bring me some coffee.—Abraham Lincoln

Cervical Syndrome

"Cervical syndrome" is a nonspecific term coined to include most of the other syndromes concerned with the head, neck, shoulders, and arms. It is caused by irritation of the cervical nerve roots, the fifth and sixth being most frequently involved, and occasionally of the cervical sympathetic chain.

Clinical features consist of sensory, motor, and trophic changes that occur in any segmental distribution. Areas of pain, localized deep tenderness, and muscle spasm are usually present and result in variable degrees of limitation of neck movement. The pain may be reflexly referred to visceral and somatic structures that have the same segmental nerve root supply, or it may arise from lesions of the cervical spinal cord and of the brain, in which case it follows no definite nerve root or segmental pattern. Irritation of the cervical sympathetic nerves may give rise reflexly to dilatation of a pupil, loss of balance, circulatory changes, palpitation, or nausea.

The etiology in a large percentage of cases is traumatic, whiplash injuries being a common cause. Most injuries result in a sprain of ligamentous or capsular structures, subluxations, anteroposterior narrowing of the inter-vertebral canals, and subsequent nerve root irritation. Roentgenograms should include oblique views for delineation of foramina.

Therapy depends upon the character and locus of involvement. Diathermy followed by traction usually affords a marked degree of symptomatic relief. Other forms of heat are often helpful. Cortisone given orally may aid in some instances. Calcareous deposits in the supraspinatus or other tendons may respond to hydrocortisone-procaine injections or may require deep x-ray therapy.

Durham, Robert H.—Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York

Remedies for Epilepsy

In cases of epilepsy, it is a good plan to eat a bear's testes, or those of a wild boar, with mares' milk or water; or else to drink a wild boar's urine with honey and vinegar, that being the best which has been left to dry in the bladder. The testes, also, of swine are prescribed, dried and beaten up in sow's milk, the patient abstaining from wine some days before and after taking the mixture. The secundines, also, of a she-ass are recommended, more particularly when it is a male that has been foaled: placed beneath the nostrils of the patient, when the fits are likely to come on, this substance will effectually repel them.*

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*Pliny

Progress

Nature revolves, but man advances.—Edward Young

No one would ever have crossed the ocean if he could have gotten off the ship in the storm.—Charles F. Kettering—Sign in his office

A good storyteller is a person who has a good memory and hopes other people haven't.—Irvin Cobb

Prophylaxis of Posttransfusion Hepatitis

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From a recent epidemiological survey on the mortality of posttransfusion hepatitis in Switzerland, Stampfli[1] was led to the grave conclusion that the administration of a single unit of blood or plasma carries a mortality risk due to hepatitis alone which equals that of childbirth. This finding demands our fullest attention and sadly documents the limited success of all prophylactic methods which have so far been designed to suppress this serious complication of blood transfusions. We think it appropriate, therefore, to review the labour devoted to that problem in the past by the Swiss Red Cross Blood Transfusion Service, to define present policies and, if possible, to formulate some guidelines for the future.

In 1949 the newly founded Central Laboratory of the Transfusion Service initiated the production of dried plasma in Switzerland. An intensive study of the problems of hepatitis transmission became mandatory almost at once. To begin with, the plasma from 20 to 30 whole blood donations was pooled to batches of six liters. Follow-up studies[2] revealed the incidence of hepatitis among the recipients of this preparation to be 2.2% relative to the number of units administered. American reports prompted us to subject the plasma to ultraviolet irradiation prior to lyophilization. Technical reasons necessitated a simultaneous increase of the batch size to 20 liters, or 50 to 70 blood donations. The effects of the irradiation were not spectacular. The incidence of hepatitis among the recipients of irradiated dried plasma remained at 1.1% relative to the number of units administered.[3] It was manifestly indefensible to continue the distribution of such a preparation to the medical profession.

At the same time, however, several serologists fortunately reported that plasma containing only agglutinating anti-A- and anti-B-antibodies could be administered to recipients with these blood groups without any risk. Hemolytic transfusion reactions occurred only when the anti-A- and anti-B-antibodies contained in the donor plasma activated complement, thus becoming active as isohemolysins.[4] These observations recorded during transfusion of blood group O to group A or B recipients and concerning the different effects of hemolyzing and non-hemolyzing blood-group antibodies furnished the basis for the production of single-donor dried plasma, which can be administered irrespective of the recipient's blood group. From 1955 onward, the Swiss Red Cross Transfusion Service has produced only single-donor dried plasma which is tested solely for the absence of isohemolysins, whereas no consideration is given to the isoagglutinin titer.[5] This preparation has proved safe as to hemolytic reactions. The risk of hepatitis transmission equals that of whole blood. It established itself rapidly and is still frequently used.

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*From the Central Laboratory of the Swiss Red Cross Blood Transfusion Service in Berne, Switzerland.

Fractionation

The fractionation of plasma to albumin and γ-globulin by means of the alcohol technique developed by Cohn was initiated soon after the production of dried plasma. As to the risk of hepatitis, albumin was already unsurpassed at that time, since it could be made hepatitis-proof by pasteurization at 60°C for 10 hours. Thus it was evidently desirable to evolve methods permitting a similar treatment of plasma. The problem was the selective removal of the heat-labile globulins. It was successfully solved in 1954 by Nitschman and Kistler[6] by total desalting of plasma with ion exchange resins. The "pasteurized plasma protein solution" consisting of albumin and the heatstable globulins was thus inaugurated, gained favor rapidly and proved to be hepatitis-proof. In the meantime, the laborious original version of Cohn's alcohol fractionation method was simplified and made less costly.[7] In order to isolate the γ-globulin contained in the original pasteurized plasma protein solution we abandoned the total desalting procedure in 1958. Pasteurized plasma protein solution was replaced by a 4% albumin solution which was introduced as "pasteurized plasma protein solution II". This preparation has largely supplanted dried plasma and was subsequently introduced in many countries under the general name of pasteurized plasma protein fraction.

In 1957 the basic concept behind the preparation of single-donor dried plasma was applied to that of fraction I.[8] The fractionation procedure was transferred from the pool to the individual bottle. In this way, a fraction-I preparation originating from two donors only was obtained, which is very effective in fibrinogen deficiency states and especially in patients with type A hemophilia. The risk of hepatitis transmission equals that incurred with two units of whole blood. In hemophiliacs it has proved to be surprisingly low; of 90 hemophiliacs who have received some 4,000 units of this preparation over the years, a single patient has suffered one minor episode of hepatitis. More recently we have replaced this two-donor antihemolytic factor preparation by a more active concentrate which is obtained by cryoprecipitation of plasma from eight donors. This antihemolytic factor concentrate, which is based on the procedure developed by Pool, is also lyophilized and thus suitable for prolonged storage.

Screening of Donor

All approaches designed to pick out the carriers of the virus and to exclude them as donors have been exploited to the full. From 1952 on, all donors with a history of infectious hepatitis have been excluded as donors of whole blood, plasma and fraction-I preparations, irrespective of the silent interval following their jaundice. Their plasma is employed for the production of albumin and γ-globulin.

Over the years we have tested all methods which might detect virus carriers by biochemical signs of liver dysfunction. The bilirubin level and the various serum lability tests proved unsuitable for the detection of anicteric hepatitis, the falsely positive and negative results being much too frequent. At one time we hoped to achieve better results by the systematic screening of the serum transaminase levels, especially that of glutamic pyruvic transaminase.[9] It is generally accepted that this enzyme is a valid indicator of subclinical liver damage. Unfortunately, results obtained in the Netherlands 10 suggest that the transaminase screening is of scant value for the prophylaxis of posttransfusion hepatitis. Apparently, contact carriers of the hepatitis virus without clinical or biochemical signs of disease are a more important source of infection than was hitherto assumed. Nevertheless, we have retained the transaminase screening, since it does undoubtedly detect liver damage in the early stage among the donors, who may then receive adequate treatment. The glutamic oxaloacetic-transaminase screening test developed by Rencher and Beeler[11] has proved to be simple, cheap and suitable for mass screening. If the reaction is dubious or positive, we determine the glutamic oxaloacetic-transaminase and glutamic pyruvic transaminase activities quantitatively. Blood showing activities in excess of 20 I.U. is reserved for plasma fractionation. Donors with glutamic oxaloacetic-transaminase and/or glutamic pyruvic transaminase activities exceeding 40 I.U. are referred to their family physician for further examination and treatment.

Conclusions

Altogether, then, the results of prophylactic measures designed to minimize the risk of posttransfusion hepatitis remain disappointing. For this reason, every physician who intends to treat a patient with whole blood, plasma or fraction-I preparations must weigh the expected benefits most carefully against the possible damage. Furthermore, since a fatal outcome of posttransfusion hepatitis is nearly always associated with severe underlying disease, especially preexisting liver damage, gastrointestinal afflictions or malignancy, it becomes mandatory to evaluate the prophylactic effects of repeated large doses of γ-globulin in high-risk patients belonging to these categories. If recent reports suggesting a limited value of such measures are confirmed by further studies, an attempt should be made to reduce the risk of posttransfusion hepatitis in high-risk patients by the exclusive use of washed erythrocytes.

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How do You Learn?

A wise man learns by experience of others. An ordinary dub learns by his own experience. A fool learns by nobody's experience.—Prairie Farmer

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High or Low

A man may be level-headed, but it's also important to know how low the level is.—Banking

Anger as Therapy for Rheumatoid Arthritis

The great physician Rhazes was summoned to Transoxiana to attend the Amir Mansur, who was suffering from a rheumatic affection of the joints which baffled all his medical attendants. On arriving at the Oxus, Rhazes was so much alarmed at its size and the small and fragile appearance of the boat in which he was invited to embark that he declined to proceed further, until the King's messengers bound him hand and foot, threw him into the boat, and carried him across by force.

On reaching Bukhara he tried various methods of treatment on the Amir without success. Finally he said to him, "Tomorrow I shall try a new treatment, but it will cost you the best horse and the best mule in your stables." The Amir agreed and placed the animals at his disposal. Next day Rhazes brought the Amir to a hot bath outside the city, tied up the horse and the mule, saddled and bridled, outside, and entered the hot room of the bath alone with his patient, to whom he administered douches of hot water and a draught which he had prepared "till such time as the humours in his joints were matured. Then he went out, put on his clothes, and, taking a knife in his hand, came in, and stood for a while reviling the Amir, saying, 'Thou didst order me to be bound and cast into the boat, and didst conspire against my life. If I do not destroy thee as a punishment for this, my name is not Muhammad ibn Zakariyya!' The Amir was furious, and, partly from anger, partly from fear, sprang to his feet." Rhazes at once fled from the bath to where his servant was awaiting him outside with the horse and the mule, rode off at full gallop, and did not pause in his flight until he had crossed the Oxus and reached Merv, whence he wrote to the Amir as follows:

"May the life of the King be prolonged in health and authority! Agreeably to my undertaking I treated you to the best of my ability. There was, however, a deficiency in the natural caloric, and this treatment would have been unduly protracted, so I abandoned it in favour of psychotherapeusis, and, when the peccant humours had undergone sufficient coction in the bath, I deliberately provoked you in order to increase the natural caloric, which thus gained sufficient strength to dissolve the already softened humours. But henceforth it is inexpedient that we should meet."

The Amir, having recovered from his anger, was delighted to find himself restored to health and freedom of movement, and caused search to be made everywhere for the physician, but in vain, until on the seventh day his servant returned with the horse and mule and the letter cited above. As Rhazes persisted in his resolution not to return, the Amir rewarded him with a robe of honour, a cloak, a turban, arms, a male and female slave, and a horse fully caparisoned, and further assigned to him a yearly pension of 200 gold dinars and 200 ass-loads of corn.*

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*Edward G. Browne: Arabian Medicine, 1921.

There is no such thing as a dangerous woman; there are only susceptible men. —*Joseph Wood Krutch*

It is a great misfortune neither to have enough wit to talk well nor enough judgment to be silent.—*Jean de La Bruyere*

In-Vivo Studies of Cellular Proliferation*

The Use of Mitotic Figures

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THE QUANTITATIVE EVALUATION of cellular proliferation, differentiation, transformation, migration and death promises to open up new perspectives in physiology and pathology. Vast efforts have been made in the past, particularly during the last decade, to improve and refine methods for investigation of the above mentioned processes, both *in vitro* and *in vivo*. It has been clearly realized that although many problems of cellular kinetics may be approached by studying *in-vitro* systems or by working with experimental animals, it will undoubtedly be necessary to do *in-vivo* studies on human beings if a precise knowledge of such features as the time parameters guiding cellular proliferation in man is one's objective.[8,16] Since information of this kind appears highly desirable in hematology, oncology, radiology, immunology and many other specialties, it may be appropriate to discuss briefly to what extent *in-vivo* studies of cellular kinetics are practicable in man.

The development of high resolution autoradiography[1,3,11] and the introduction of specific deoxyribonucleic acid precursors such as tritiated thymidine (T^3H)[4,17,18] have led to such a rapid increase in experimental means that we have chosen to limit this discussion to methods based on the evaluation of mitotic figures. This limitation will, of course, center the present consideration on techniques apt to investigate the proliferative characteristics of cells within a given cell line or cell system, disregarding other important aspects of cellular kinetics such as migration, cell death, etc.

Definition and Description of a Cell System

Before making an attempt to characterize the importance of mitotic figures for *in-vivo* studies of cell proliferation within a particular cell line or cell system, a short description of a hypothetical and greatly simplified cell sys-

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tem will be given to illustrate some of the methodological limitations discussed later (Figure 1).

There is no generally accepted definition of the term "cell system" or "cell line." Obviously a cell system or cell line within a living organism represents a functional unit satisfying clearly defined needs, at least under physiological conditions.

The Cell Compartments

A cell system may be divided into several compartments, each compartment containing a class of cells distinguished from other cells in the system. The distinction may be based on function, morphology and location.[12] If functional criteria are used to subdivide a proliferative cell system the following typical compartments may be distinguished:

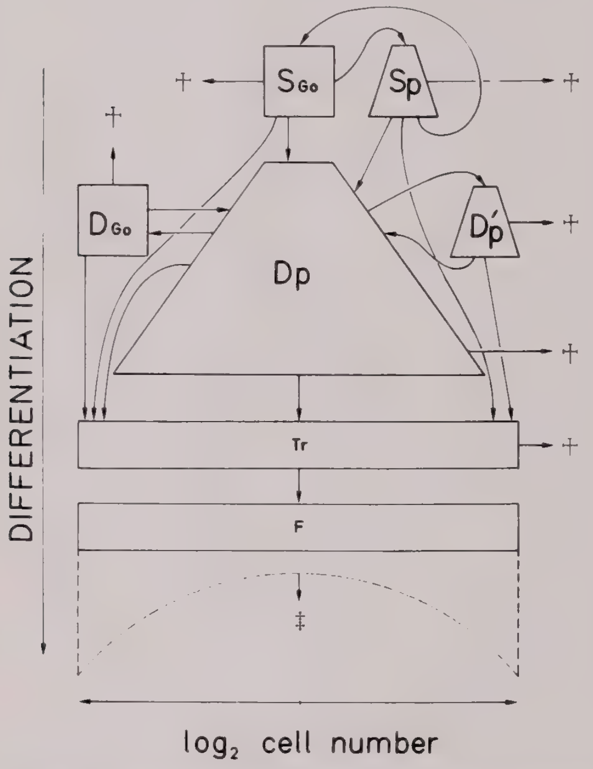

Fig. 1—Hypothetical scheme of a proliferating cell system. S_{G_0}: G_0 compartment of stem cells. S_p: generative compartment of stem cells. D_{G_0}: G_0 compartment of differentiating and proliferating cells. D_p: generative compartment of differentiating and proliferating cells. D_p': generative compartment of partially differentiated cells which do not continue to differentiate during proliferation. T_r: transitional compartment. F: functional compartment. ‡: functional compartment if cell death occurs at random. †: cell loss due to cell death.

—G_0 compartment(s) consisting of cells which do not actually proliferate but retain their ability to do so if stimulated.

—generative compartment(s) consisting of cells which may be in at least four different stages of the cell cycle:

G_1: postmitotic = presynthetic phase.

S: deoxyribonucleic acid synthesis phase usually equated with the period during which cells incorporate specific deoxyribonucleic acid-precursors.

G_2: postsynthetic = premitotic phase.

M: mitotic phase.

—the transitional compartment formed by cells in transition from proliferation to maturity.

—the functional compartment with functional (= mature) cells.

The end cell compartment comprises all cells in a cell system which have lost the ability to divide.

It should be clearly realized that compartments defined by functional criteria are not necessarily identical with those defined morphologically: thus G_0 cells and cells of a generative compartment may not be distinguished on morphologic grounds; and cells of one morphologically defined compartment may belong to two or more generative compartments.

Parameters of Compartments

In order to describe a cell system containing several compartments, information on the following parameters is needed:[12]—the relative or absolute size of the compartments,—the transit times (=time elapsed between entering and leaving a compartment),—the fluxes (=number of cells passing a particular compartment boundary in a particular direction per unit of time) and—the birth and death rates (=numbers of cells dividing or dying per cell number and unit of time in a given compartment).

Since not all cells do behave in exactly the same way and since at least some of the parameters enumerated can be expressed only in the form of distributions rather than absolute values, a complete description of a cell system is very difficult. The question therefore arises, whether at least one or the other of the parameters just enumerated were amenable to assessment in the intact human organism. If, within a given cell system, certain proliferative characteristics remain more or less constant from individual to individual, an accurate description of a cell system might gradually be realized. With this admittedly very optimistic view in mind, the relative reliability of a few methods used to investigate the proliferative pattern of a given cell line will now be discussed.

Mitotic Figures and the Evaluation of Cellular Proliferation

The relative number of mitotic figures has long been taken as an indicator of the proliferative activity within a given cell class. As discussed below, a combined determination of the mitotic index and the mitotic time formed the basis for many classical investigations of cellular proliferation (reviewed by Leblond and Walker, 1956). These methods do not require the *in-vivo* administration of radioactive materials for labeling purposes nor do they necessitate repeated sampling over prolonged periods of time.

The introduction of autoradiography and the availability of T^3H made it possible to investigate more accurately not only cell proliferation but also cell differentiation, maturation and death.[3] Although cell proliferation could now be studied without referring to mitotic figures, it soon became apparent that accurate measurements of cell proliferation *in vivo* still required the presence of mitotic figures.

Cellular Proliferation without Radioactive Compounds

Determination of the "Mitotic Index"

The mitotic index (MI), the fraction of a cell population in mitosis, is a function of the duration of mitosis (T_m) and of the average time (T) which the cells spend in the population studied: $MI = f\ (T_m/T)$ (Killmann, Cronkite, Fliedner, Bond and Brecher, 1963).

Combined determinations of mitotic indices and mitotic time have therefore been used to compute turnover times (= time taken for the replacement of a number of cells equal to that in the whole population: Leblond and Walker, 1956) and/or generation times (T_g = average duration from completion of one mitosis to completion of the following mitosis) by transforming the equation above to $T = f\ (T_m/MI)$.

One of the *major limitations* in the use of mitotic indices is related to the fact that it may be extremely difficult to assign dividing cells to a given population of cells in interphase (Leblond, 1959). This may be due to a lack of cytoplasmatic differentiation leading to an inability to establish a relation between cells in mitosis and cells in interphase. If cytoplasmic differentiation is adequate, other difficulties arise. As mentioned earlier, functional compartments are often not identical with morphologically defined cell classes within a given proliferating cell system. Furthermore, if a generative and a G_0 or end cell compartment cannot be differentiated morphologically, it will not be possible to relate the number of mitotic figures counted to the so-called growth fraction of the cell population studied, and one is obliged to determine a mitotic index for a morphologically but not functionally homogenous class of cells. This is a serious limitation since undetectable changes in the composition of such a class of cells might occur.

Even if all cells within a morphologically determined compartment do proliferate, the exact position of mitosis with respect to the morphologically defined compartment boundaries has to be known if one desires to com-

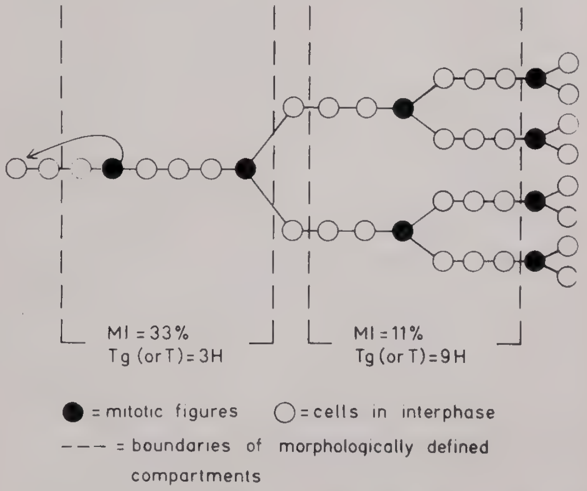

Fig. 2—The influence of the position of mitosis with respect to morphologic compartment boundaries on mitotic index determinations and computations based thereon. Assumed T_g = four hours, assumed turnover time (T) for each compartment = six hours.

pute turnover times from mitotic index and mitotic time data (Figure 2).[6]

Several other *factors may bias mitotic index* determinations: —diurnal variations of the proliferative activity and other disturbances of the steady state, —variability in the ratio of proliferating to nonproliferating cells due to sampling procedures, —loss of mitotic figures due to inadequate staining techniques, difficulties in recognizing early pro- and/or late telophases, preferential destruction and/or uneven distribution of mitotic figures on smear or squash preparations, —intracompartmental cell death.

This brief enumeration of biasing factors demonstrates well how limited the reliability of mitotic index data is for an evaluation of cellular proliferation *in vivo*. As discussed below, classic mitotic time calculations are also based on mitotic index determinations. It is therefore clearly seen that turnover and/or generation time computations from classic mitotic index and mitotic time data can be of only limited value.

Determination of the "Mitotic Time"

Mitotic time is the duration from the first recognizable prophase to the latest recognizable telophase.

Several classic methods have been used to determine mitotic time *in vivo* (Leblond, 1959; Dustin, 1959). The majority of these are based on at least two mitotic index determinations, one before and one after intervening, by chemical (e.g., colcemide) or physical means (x-rays), with the progression of proliferating cells through G_2 and M. All restrictions in the use of mitotic indices therefore apply also to classic mitotic time determinations. Incomplete blocking of cellular progression, toxic effects of the blocking agents used and inadequate timing of the second sample with respect to the administration of the blocking agent may also limit the validity of conventional mitotic time assessments.

Cellular Proliferation in vivo with T^3H

The methods to be discussed here are all based on the fact that mitotic figures represent a morphologically well-defined, short-lasting stage of the cell cycle characterized by the absence of deoxyribonucleic acid synthesis, thus permitting observation of the progression of labeled cells, after a single intravenous injection of T^3H, through this "window." The methods described require the presence of adequate numbers of mitotic figures, *in-vivo* injection of T^3H and serial sampling thereafter. They all depend on the assumptions made whenever high-resolution autoradiography and T^3H are used.[3]

Mitotic Labeling Index

This method was first described by Quastler and Sherman in 1959. Due to its short availability time of 15 to 20 minutes, intravenously injected T^3H will pulse-label all cells synthesizing deoxyribonucleic acid provided these cells dispose of the necessary enzymatic equipment to incorporate T^3H.[14] In a population of proliferating cells the cells in S which were marked by T^3H will leave S, progress through G_2 and enter M. Unlabeled mitotic figures will then be replaced by labeled ones and the mitotic labeling index, that is the relative number of mitotic figures labeled, will rise, form a "plateau" and start to fall again as soon as unlabeled cells which were in G_1 at the time of T^3H injection enter into mitosis. Theoretically the mitotic labeling index should then fall to zero and, later on, when the initially labeled cells divide again, it should rise to form a second "wave." As a rule, an analysis of the mitotic labeling index variation after a single injection of T^3H permits us to evaluate the duration of G_2 and S, especially if the majority of daughter cells continue to proliferate upon completion of the first division, T_g and the duration of G_1. In addition, information regarding the distribution of G_2, S and generation times of individual cells may be obtained; furthermore, it is possible to detect the presence of reutilization of labeled deoxyribonucleic acid.[20]

The results obtained by an analysis of mitotic labeling index data are not influenced by factors that bias mitotic index determinations, such as loss of mitotic figures, variations of the ratio of proliferating to nonproliferating cells, position of mitosis with respect to the morphologically defined compartment boundaries and intracompartmental cell death. They are influenced, however, by straggling (= deviation in time from a "rigorously-timed orderly progression" of cells through mitosis[9]), by disturbances of the steady state, by the difficulties arising from the inability to assign mitotic figures with minimal cytoplasmic differentiation to a given population of cells in interphase, and by the inability to clearly distinguish, morphologically, between mitotic figures belonging to cell populations with different proliferative characteristics.[15,20] Another limitation of this method is observed if a morphologically homogenous class of cells is composed of a proliferating and relatively large pool of G_0 cells: if, upon completion of mitosis, all proliferating cells enter the G_0 pool, and if, on the other hand, G_0 cells are triggered at random to enter G_1, no or only a minimal second wave will be found in the mitotic labeling index curve.

Midprophase-Midtelophase Time

Although rough estimates of mitotic time can be obtained by extrapolating the steepest slope of the initial rise of the mitotic labeling index after a single injection of T^3H, the best estimates of mitotic time *in vivo* are based on an analysis of the variation of separate pro- and telophase labeling index curves after pulse-labeling with T^3H.[2,10] From the experimentally determined mean "midprophase-midtelophase time" it is possible to compute mitotic time either graphically or mathematically. This method requires a precise morphologic definition of prophases and telophases and necessitates the existence of a rather constant ratio between the relative numbers of pro-, meta-, ana- and telophases.

Median Grain Count per Labeled Mitotic Figure

This method was first used in combination with mitotic labeling index determinations.[5,20] It is based on the observation that after a single injection of T^3H the mean or median grain count per labeled mitotic figure (MGC/LMF) varies with time in such a way that initially two peaks, representing periods of maximal deoxyribonucleic synthesis rate during the S phase, appear. As a rule, the second peak is only half as high as the first, indicating that daughter cells with half the amount of deoxyribonucleic label have recycled and are dividing. The time interval between the two peaks of the MGC/LMF curve can therefore be taken as a measure of T_g.

Besides being biased by the limiting factors enumerated while referring to the mitotic labeling index method, this technique is influenced by the autoradiographic efficiency[3] and by the fact that grain counts, particularly if more than 30 to 50 grains per cell are seen, become inaccurate. It is evident that this method will not furnish any information on the duration of single cell cycle phases. It will, however, permit one to evaluate roughly the rate of T^3H-incorporation during the S phase.

Conclusions and Summary

It has been shown that the more laborious methods of cell proliferation *in vivo*, developed during the last decade, necessitating the evaluation of mitotic figures, the *in-vivo* administration of radioactive deoxyribonucleic precursors and serial sampling thereafter are more reliable than any method based on mitotic index determinations. In particular, a combination of serial mitotic labeling index (MLI) and mean or median grain count per labeled mitotic figure (MGC/LMF) determinations after a single T^3H injection has proved to be a powerful tool in the assessment of cellular proliferation.

These methods, obviously, cannot be used for clinical purposes, except perhaps for a few, highly selected cases where such a study may be justified as long as one can hope to find, within a well-defined cell system, a certain constancy of essential proliferative characteristics from individual to individual.

If such a constancy does exist, it should be possible to gradually accumulate enough information to provide a more rational basis for essential clinical topics such as cancer therapy and immunosuppression. The painstaking search for mitotic figures, therefore, has not become obsolete as yet; on the contrary, it appears more rewarding today than ever before.

References may be secured from the author.

Clinical Notes of Razi*

The Treatment of Pyelitis

"Abdullah ibn Sawda used to suffer from attacks of mixed fever, sometimes quotidian, sometimes tertian, sometimes quartan, and sometimes recurring once in six days. These attacks were preceded by a slight rigor, and micturition was very frequent. I gave it as my opinion that either these accesses of fever would turn into quartan, or that there was ulceration of the kidneys. Only a short while elapsed ere the patient passed pus in his urine. I therefore informed him that these feverish attacks would not recur, and so it was.

"The only thing which prevented me at first from giving it as my definite opinion that the patient was suffering from ulceration of the kidneys was that he had previously suffered from tertian and other mixed types of fever, and this to some extent confirmed my suspicion that this mixed fever might be from inflammatory processes which would tend to become quartan when they waxed stronger.

"Moreover the patient did not complain to me that his loins felt like a weight depending from him when he stood up; and I neglected to ask him about this. The frequent micturition also should have strengthened my suspicion of ulceration of the kidneys, but I did not know that his father suffered from weakness of the bladder and was subject to this complaint.

"So when he passed the pus I administered to him diuretics until the urine became free from pus, after which I treated him with *terra sigillata,* Boswellia thurifera, and Dragon's Blood, and his sickness departed from him, and he was completely and quickly cured in about two months. That the ulceration was slight was indicated to me by the fact that he did not complain to me at first of weight in the loins. After he had passed pus, however, I enquired of him whether he had experienced the symptom, and he replied in the affirmative. Had the ulceration been extensive, he would of his own accord have complained of this symptom. And that the pus was evacuated quickly indicated a limited ulceration. The other physicians whom he consulted, however, did not understand the case at all, even after the patient had passed pus in his urine."

In spite of several difficulties both verbal and material, which I have not yet been able to solve to my satisfaction, the general nature of this case seems fairly clear. The patient suffered from intermittent and irregular attacks of fever preceded by slight rigors, which, in a land infested with ague, were diagnosed and treated as malarial, though really septic in origin. Razi himself at first took this view, but subsequently, observing the presence of pus in the urine, diagnosed the case as one of pyelitis, and treated it accordingly with success.†

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*Razi (Rhazes)—Persian-born Mohammedan physician (850-923).

†Edward G. Browne: Arabian Medicine, 1921.

Short Biography

Apron strings, heart strings, purse strings, harp strings.—Howard Newton

He uses statistics as a drunken man uses lampposts—for support rather than for illumination.—Andrew Lang

Electronic Data Processing in the Clinical Laboratory

A Routine System for Clinical Chemistry

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THE NUMBER OF LABORATORY tests in clinical chemistry doubles every three to five years.[1-3] To balance this increasing work load automation and electronic data processing were introduced. Depending on the type of laboratory, between 10 and 40% of the total working time is used for clerical work. Introduction of electronic data processing should reduce this time substantially and free technicians for laboratory work proper.

A routine electronic data processing system was installed at the chemistry laboratory of the Children's Hospital in August 1967; in January 1968 it was extended to the major medical and surgical services. The system was designed not only to reduce clerical work in the laboratory, but also to facilitate interpretation of results and to eliminate any type of transcribing errors on the wards.

Description of the System

Electronic Data Processing

The Inselspital is a University hospital with approximately 1,200 beds and large outpatient departments. Seven routine clinical chemistry laboratories are distributed over the whole area, but they will be centralized in a new building within this next year. In 1967, 316,000 quantitative chemical analyses were performed.

The electronic data processing program was developed in close cooperation with the electronic data processing center at the University of Berne, located approximately one mile from the hospital laboratories. Punching of cards is done peripherally in the laboratories on two card punchers; processing of the punched cards is performed at the university center. A Bull Gamma 30 computer with 40,000 magnetic core positions, six magnetic tape stations, a card puncher and a printer are used. Processing is done daily at 5 p.m. and takes about 15 minutes for 1,000 tests.

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Input Forms

Two input forms are used: a master card and a test card. The master identification card (Table 1) contains the administrative information on each patient. It is keypunched on the day the patient is admitted to the hospital. All master cards are filed alphabetically in a master card file. On discharge the master card is removed from the master card file. It can then be used for other purposes, such as the generation of a diagnostic index or for statistics.

The layout of the test result cards is shown in Table 2. A large number of individual cards for each test are prepared by gang-punching the test code into the test code columns. These cards are kept in a test code file.

Output Forms

Three types of output forms are used. On a "laboratory test list" results appear, sorted by tests. These forms are kept in the laboratory as a record. A "list of abnormal results" is prepared daily for each physician in charge of a ward, containing the results of all the tests performed on patients who had at least one abnormal result. Finally, "case record forms" are printed daily for each patient on whom analyses have been performed; these are cumulative and contain all the results for the patient. Whenever a new form arrives on the ward the old one is discarded.

TABLE 1
Master Identification Card

Card columns	Information
1-6	Patient admission number
7-12	Date of birth
13-42	Full name (surname and first name)
43	Sex
44-49	Ward
50-55	Date of hospital admission
56-61	Date of hospital discharge

TABLE 2
Test Result Card

Card columns	Information	Source
1-6	Patient admission number	Duplicated from master identification card
7-12	Date of birth	
13-42	Full name	
43	Sex	
44-49	Ward	
50-55	Date of hospital admission	
56-61	Date of specimen receipt	Added by keypunch program card
62-67	Test code	Prepunched
68-73	Time of specimen receipt (emergencies only)	Added by keypunch operator
74-79	Test result	

Test Code

For test description and identification a test code was designed. It is alphanumerical* and consists of six code units. A first letter describes the type of laboratory, e.g., C for chemistry. The second and third letters state the component analyzed, e.g., GL for glucose. The fourth position is numerical and identifies the method used, e.g., 1 for a glucose oxidase/peroxidase procedure. The fifth letter states the system analyzed, e.g., P for plasma. The sixth letter is used for supplementary information, e.g., C for capillary. A detailed description of the code is given elsewhere.[4]

Laboratory Procedure

The laboratory procedure is shown in Figure 1. Specimens and request cards are received in the laboratory. The corresponding master card is drawn from the master card file. For each test required, corresponding prepunched test cards are put behind the master card. Patient information is duplicated from the master card into all the corresponding test cards. The date is punched automatically from a program card on the card punch. In this way a set of written and punched cards containing administrative information, test code and date is obtained automatically. After analysis has been performed the result is manually written on the punch card. No worksheets are prepared, but the test cards are used directly as work sheets. Before computer processing the results are keypunched into the card.

Computer Processing

The daily routine consists of four special purpose programs (Run 1 through Run 4) and two software sorting programs (Sort-1, Sort-2). In Run 1 the result cards are read and checked for certain types of errors, such as letters instead of numerals for the date of birth, impossible test codes, and completeness of information. An error list is then printed. The information on the correct cards is taken on magnetic tape. The records then are sorted according to the date of analysis and the type of test (Sort-1). This yields a sorted preliminary result tape.

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*See Test Your Word Score Page 89.

In Run 2 the results are checked for normality in respect to age and sex of the patients. First the age of the patient is calculated from birth date and date of analysis. Then the result is compared with age-and-sex-adjusted normal values, which are stored on the "normal range tape." Slightly abnormal results are marked by one asterisk, markedly abnormal values by two asterisks. At the same time the age-and-sex-corrected normal range is entered. Each record with the new information added in Run 2 yields a record on the result tape.

Simultaneously, lists of daily results are produced for each test performed (Figure 2).

In Sort-2 the records on the result tape RB2 are sorted according to patient identification (i.e., ward, patient's number, patient's admission date), date and time of analysis. In Run 3 a list with the results of those patients who had at least one abnormal result (Figure 3) is prepared for each ward. In the same run the setup of tape RB2 is changed, giving a mutations tape.

In Run 4 the case record forms are produced. All the information on each patient is stored on the patient's tape, which is daily updated by combining information from the old tape and the mutations tape, thereby producing a new patient's tape. Every day a new case record sheet is printed which substitutes for the old one (Figure 4). Results are printed cumulatively, the new record sheet containing all the results of the preceding days on which analyses were performed. If analyses have been done on more than five days, then a new record sheet is started, on which a special comment not to delete the old sheet is printed by the computer.

Once a month the patient's tape is updated by a special program. Patients who have been discharged are taken off the patient's tape. Their results are printed on a monthly report list.

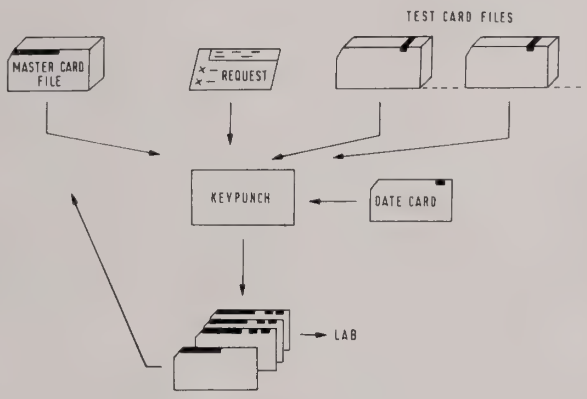


Fig. 1—Preparation of test cards.

Laboratory Results

Test : CKA1PV : Plasma-Potassium

Date	Time	Patient Number	Date of Birth	Name	Sex	Ward	Results
12-3-68		204328	7- 5-67	Aegerter Urs	M	002721	3.85
		206938	29- 8-55	Berli Alberto	M	002744	3.05
		204128	16-10-50	Bieri Marco	M	002755	4.9
		223807	7-12-62	Cueni Josette	F	002740	4.2
		204618	28- 9-65	Gasser Marie	F	002723	3.45

Fig. 2—List of laboratory results for the laboratory.

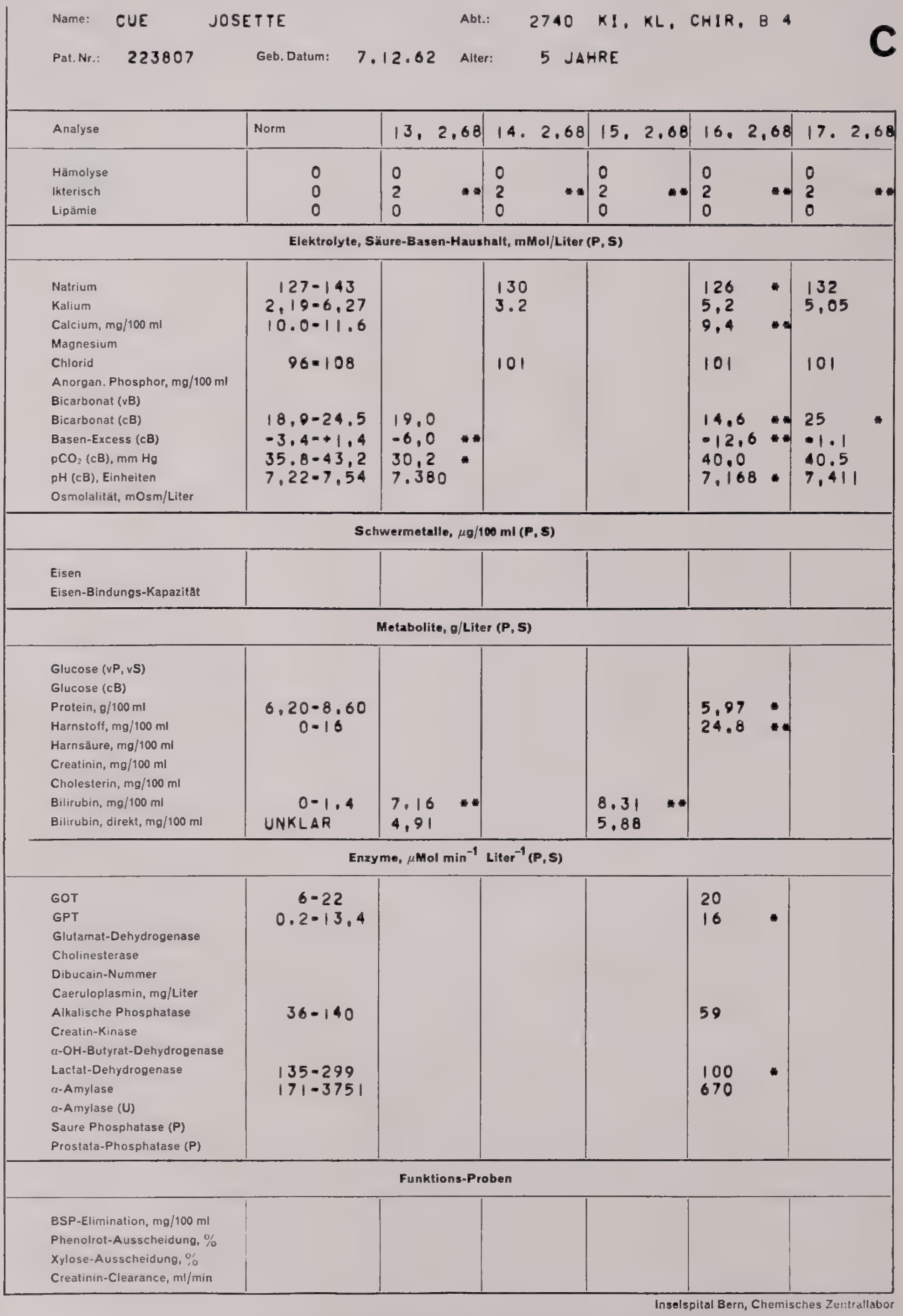
Patients with Abnormal Results

Name	Date of birth	Date of results	Time Test	Normal	Results
Rothen Martha	12-5-06	12-3-68	Kalium	2.58-6.50	4.8
			Chlorid	96-108	105
			Natrium	127-143	134
			Bilirubin	0-1.4	3.35**
			Cholesterin	134-285	279

Fig. 3—List of abnormal results for the house officers.

Advantages

Only a few electronic data processing systems for laboratory use have been described[3,5-9] though many are probably in some phase of study, development or trial. Most of these systems are using a computer within the laboratory or hospital area. Since this was impossible for financial reasons, we decided to try to use the computer of the university center. This has actually proven to be an advantage for the development and the routine use of electronic data processing. Available at these centers are experienced personnel not usually available within the hospital range. Today all



Name: CUE JOSETTE
Abt.: 2740 KI, KL, CHIR, B 4
Pat. Nr.: 223807
Geb. Datum: 7.12.62
Alter: 5 JAHRE

C

Analyse	Norm	13, 2,68	14. 2,68	15, 2,68	16, 2,68	17. 2,68
Hämolyse	0	0	0	0	0	0
Ikterisch	0	2 **	2 **	2 **	2 **	2 **
Lipämie	0	0	0	0	0	0
Elektrolyte, Säure-Basen-Haushalt, mMol/Liter (P, S)						
Natrium	127-143		130		126 *	132
Kalium	2,19-6,27		3.2		5,2	5,05
Calcium, mg/100 ml	10.0-11.6				9,4 **	
Magnesium						
Chlorid	96-108		101		101	101
Anorgan. Phosphor, mg/100 ml						
Bicarbonat (vB)						
Bicarbonat (cB)	18,9-24.5	19,0			14,6 **	25 *
Basen-Excess (cB)	-3,4-+1,4	-6,0 **			-12,6 **	-1.1
pCO_2 (cB), mm Hg	35,8-43,2	30,2 *			40,0	40.5
pH (cB), Einheiten	7,22-7,54	7.380			7,168 *	7,411
Osmolalität, mOsm/Liter						
Schwermetalle, µg/100 ml (P, S)						
Eisen						
Eisen-Bindungs-Kapazität						
Metabolite, g/Liter (P, S)						
Glucose (vP, vS)						
Glucose (cB)						
Protein, g/100 ml	6,20-8.60				5,97 *	
Harnstoff, mg/100 ml	0-16				24.8 **	
Harnsäure, mg/100 ml						
Creatinin, mg/100 ml						
Cholesterin, mg/100 ml						
Bilirubin, mg/100 ml	0-1,4	7,16 **		8,31 **		
Bilirubin, direkt, mg/100 ml	UNKLAR	4,91		5,88		
Enzyme, µMol min^{-1} $Liter^{-1}$ (P, S)						
GOT	6-22				20	
GPT	0.2-13,4				16 *	
Glutamat-Dehydrogenase						
Cholinesterase						
Dibucain-Nummer						
Caeruloplasmin, mg/Liter						
Alkalische Phosphatase	36-140				59	
Creatin-Kinase						
α-OH-Butyrat-Dehydrogenase						
Lactat-Dehydrogenase	135-299				100 *	
α-Amylase	171-3751				670	
α-Amylase (U)						
Saure Phosphatase (P)						
Prostata-Phosphatase (P)						
Funktions-Proben						
BSP-Elimination, mg/100 ml						
Phenolrot-Ausscheidung, %						
Xylose-Ausscheidung, %						
Creatinin-Clearance, ml/min						

Inselspital Bern, Chemisches Zentrallabor

Fig. 4—Cumulative case record form.

the routine computer work is done by the personnel of the computer center, while development and programming is done at the hospital unit. Good cooperation between the hospital and the computer center is necessary for the successful implementation of hospital programs. It is important that electronic data processing for hospitals obtain priority.

Contrary to many other efforts in electronic data processing our approach has not been very costly. The whole project was developed by the authors within about three years' time. The planning phase lasted about two years and was used chiefly to study existing electronic data processing systems. It took about one additional year to design all the forms needed and for programming. No trial period was needed; the system proved practicable from the first day.

Reduction of Clerical Work

Previously the name of a patient used to be written two to five times per test and two to 100 times per hospital stay. Estimates in our laboratories have shown that approximately 30% of the whole time was used for clerical work. Now the name of the patient is written only once by preparing the master card on the admitting day, thus reducing the clerical work load from about 30% to about 10% of the total working time.

Elimination of Spelling Errors

Errors in the spelling of names and wards were previously quite frequent, but are now eliminated completely because all identification data are reproduced from a master identification card.

Reduction of the Work Load on the Ward

In most conventional systems and even in some electronic data processing systems the results are given to the ward on a type of form containing the results of one day only and are then transcribed manually on a chronological and cumulative laboratory report sheet. Depending on the hospital this transcription is done by nurses, house officers or interns.

Elimination of Transcription Errors on the Wards

It must be assumed that errors occurred at the transcription stage on wards. By using computer-printed output forms this type of error has become impossible.

Simplification of Record Keeping

In conventional systems, records of laboratory reports are kept in books or files. These systems are space-consuming and make it difficult to locate old reports. The monthly report system permits the storage of results in minimal space; in addition, the magnetic tape-stored information can be used directly for research.

Automatic Production of Laboratory Statistics

The storage of laboratory results permits an automatic production of statistics. Not only the total number of tests, but also the number of tests per ward, per age group, per day, month or year, and the number of emergency tests per ward or per disease group can easily be computed.

Improvement of Quality Control

A few attempts have so far been made to improve quality control of the results by the use of a computer.[10] We are at present engaged in incorporating quality control in our system.

Improvement of Normal Ranges

It is probable that the large number of data accumulated during the years will permit a better definition of normal ranges of laboratory results. This is probably one of the crucial areas of clinical chemistry, and we hope to use our data for this particular purpose.

Advantage to Physicians

In addition to these eight features of improvement in laboratory results and in communication of the results to the physician, particular care was taken to present the results to the physicians in a more meaningful way. This was attempted by four devices:

Comparison with Normal

Each result is compared in the computer to age-and-sex-adjusted normal values. These values are printed in the first column of the case record sheet and also in the first column of the list of abnormal results.

Abnormal Results

Abnormal results are marked. One asterisk means that a result is within the confidence limits of 0.95-0.99 and two asterisks that it is definitely abnormal and outside the 0.99 confidence limits.

Aid to Rapid Diagnosis

The daily list of abnormal results supplied to each physician in charge of a ward should enable him to see important results at one glance. These sheets do not have any permanent value but are used on only one day. They should help in rapid diagnostic and therapeutic decisions.

Case Record Form

Most published systems for electronic data processing present the results in a computer-printed form to the physician. These records are often poorly legible and not in chronological order. Care was taken to design a chronological case record form which does not differ much from the conventional form but permits easy legibility and a clear picture.

Disadvantages

The following difficulties have been experienced with the system:

Errors on Master Card

Errors on the master identification card will be perpetuated on each result card and will be stored on magnetic tape. A special correction program has to be used to correct this type of error.

Ward Identification

Difficulties were encountered in regard to the ward identification of patients. Our hospital structure has been growing over many years, and new names such as department, clinic, station, ward have been introduced indiscriminately. A clear concept of hospital organization and terminology should be obtained before electronic data processing is introduced.

Age-and-Sex-Adjusted Normal Values

The most important difficulty has been the selection of age-and-sex-adjusted normal values. In some areas, e.g., enzyme concentrations, we could rely on our own established values;[11] in other cases we had to rely on values from the literature, often obtained with slightly different methods and apparatus. It is planned to revise these normal values as soon as possible.

Conclusions and Summary

Generally, the introduction of the system has been a success. Most physicians have accepted the system without reluctance and are now considering its existence as a quite obvious and natural thing.

An electronic data processing system for clinical chemistry results is described. Processing is performed on a Bull Gamma 30 computer. Special care was taken to improve the medical significance of the results, by giving age-and-sex-adjusted normal ranges for each test, by marking abnormal results by asterisks, and by printing a daily list of abnormal results for each ward and daily cumulative case record sheets for each patient.

This is the third of a series of papers on electronic data processing in the clinical laboratory. This work has been supported by The "Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung" (Projekt Nr. 3740). We would like to thank Dr. R. Hüsser, head of the computer department of the University of Berne, for his help and kind cooperation.

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9-11. May be secured from the author.

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Warnings—Watch for the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, retinal thrombosis); if present or suspected discontinue the drug immediately.

British studies reported in April 1968[1,2] estimate there is a seven- to tenfold increase in mortality and morbidity due to thromboembolic diseases in women taking oral contraceptives. In these controlled retrospective studies, involving 36 reported deaths and 58 hospitalizations due to "idiopathic" thromboembolism, statistical evaluation indicated that the differences observed between users and non-users were highly significant. The conclusions reached in the studies are summarized in the table below:

Comparison of Mortality and Hospitalization Rates Due to Thromboembolic Disease in Users and Non-Users of Oral Contraceptives in Britain.

Category	Mortality Rates		Hospitalization Rates (Morbidity)
	Age 20-34	Age 35-44	Age 20-44
Users of Oral Contraceptives	1.5/100,000	3.9/100,000	47/100,000
Non-Users	0.2/100,000	0.5/100,000	5/100,000

No comparable studies are yet available in the United States. The British data, especially as they indicate the magnitude of the increased risk to the individual patient, cannot be applied directly to women in other countries in which the incidences of spontaneously occurring thromboembolic disease may differ.

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or sudden onset of proptosis, diplopia or migraine. Withdraw medication if papilledema or retinal vascular lesions are found.

Since the safety of Ovulen in pregnancy has not been demonstrated, it is recommended that pregnancy be ruled out for any patient who has missed two consecutive periods before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule the possibility of pregnancy should be considered at the first missed period.

A small fraction of the hormone agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

Precautions—Pretreatment physical examination should include special reference to the breasts and pelvic organs, and a Papanicolaou smear.

Endocrine and possibly liver function tests may be affected by Ovulen. Therefore, it is recommended that such tests if abnormal be repeated after the drug has been withdrawn for two months.

Pre-existing uterine fibromyomas may increase in size under the influence of progestogen-estrogen preparations.

Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.

In breakthrough bleeding, and all irregular vaginal bleeding, consider nonfunctional causes. Adequate diagnostic measures are indicated in undiagnosed vaginal bleeding.

Carefully observe patients with a history of psychic depression and discontinue the drug if severe depression recurs.

Any possible influence of prolonged Ovulen therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study.

A decrease in glucose tolerance has occurred in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be observed carefully while receiving Ovulen.

Because of the effects of estrogens on epiphyseal closure Ovulen should be used judiciously in young patients in whom bone growth is not complete.

The age of the patient constitutes no absolute limiting factor, although Ovulen therapy may mask the onset of the climacteric.

The pathologist should be informed of Ovulen therapy when relevant specimens are submitted.

Adverse Reactions—A statistically significant association has been shown between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: cerebrovascular accidents, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, breast changes (tenderness, enlargement, secretion), change in weight, changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post partum, cholestatic jaundice, migraine, allergic rash, rise in blood pressure in susceptible individuals, mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme and nodosum, hemorrhagic eruption, itching.

The following laboratory results may be altered by oral contraceptives: hepatic function: increased sulfobromophthalein and other tests; coagulation tests: increase in prothrombin, Factors VII, VIII, IX and X; thyroid function: increase in PBI and butanol extractable protein bound iodine, and decrease in T^3 uptake values; metyrapone test; pregnanediol determination.

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Editorials

Salute to Berne

Switzerland with a population only half again greater than Minnesota has five times as many medical schools. Geneva, Laussane, Zurich, Basle, and Berne as part of their universities include a medical school. The faculty of one of these has provided Minnesota Medicine with this special Berne issue. The Berne Medical School, by European standards, is not old, having been founded in 1834. Fritz de Quervain, Professor of Surgery, reviewed the distinguished history of his medical school in 1934 celebrating the centennial.* He was the magnet drawing young surgeons to Berne in the early years of this century. Among them were three Minnesotans, Carl O. Rice, George Eitel and Owen Wangensteen, who studied in Berne in the late twenties. The disease they came chiefly to see was goiter. Switzerland, and particularly Berne with its low iodine mountainous environment, was the goiter capital of the world at that time. The pervasive use of iodized salt, begun in America after the work of David Marine, reached the Swiss plateau in the thirties and ended Berne's goitrous reign.

The editors of Minnesota Medicine take pride in presenting in this issue the scientific papers from Berne and thank the authors for their contributions. Many readers of Minnesota Medicine vacationing in the Switzerland mountains and valleys will visit the capital city of Berne and its famous Medical School.

Reuben Berman, M.D.
Minneapolis, Minnesota

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*Fest Schrift zur Jahnrhundertfeier de Universitat Berne. F. de Quervain. Schweiz Med Wchnscrft 64:525, 1934.

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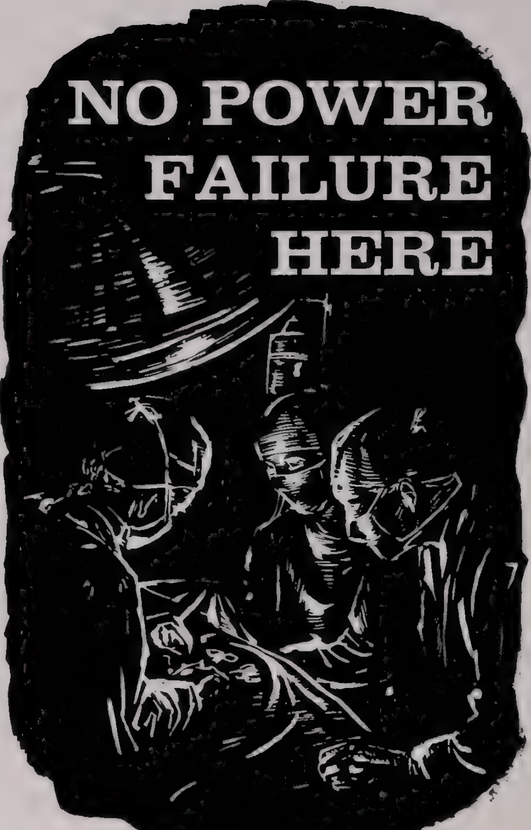
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The Department of Internal Medicine

Since January 1966 this department has been reorganized. Responsibility for patient care, internal administration and teaching are divided among three heads of division (full time professors), one of them acting as chairman. Patients are admitted at random to one of the three divisions which practice all the subspecialties of internal medicine. Except for technically specialized units (intensive care f.i.) no beds are allotted to subspecialties. The latter are represented by divisions whose members have consultant functions in the clinical divisions, except for a limited outpatient practice. The house staff in charge of direct patient care is appointed to the entire department and rotates among the three divisions; a slower rotation among the three heads of division also takes place. There is an interchange between the staffs of clinical and specialistic divisions. Three staff meetings are held per week, one of them open to members of other divisions and practicing physicians, another for the department staff only, and a third one of purely administrative nature. In the two former ones patients and subjects of common interest are discussed, while regular rounds take place within the divisions.

Research is mostly done within the specialistic divisions, consisting of the divisions for pulmonary diseases (Dr. M. Scherrer), for cardiology (Dr. H. P. Gurtner), for hematology (Dr. U. Bucher) and for gastroenterology (Dr. F. Halter). Clinical pharmacology (Dr. R. Preisig) is a joint division of the departments of pharmacology and internal medicine.

While the chairman (Dr. Wyss) is mainly in charge of administrative and academic affairs, one of the other heads of the clinical divisions (Dr. Studer) runs the thyroid research laboratory, while the other (Dr. Pauli), whose main field of research was clinical acid base metabolism, is in the process of establishing an office of research in medical education.

F. Wyss, M.D.*
H. G. Pauli, M.D.*
H. Studer, M.D.*
Berne, Switzerland

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*University of Berne, Switzerland.

Trigger Fingers

The article by Doctor Lenggenhager* concerns the vexing problem of the trigger finger. The diagnosis of trigger finger, based on the complaints of stiffness and snapping and confirmed by the presence of tenderness over the proximal pulley of the tendon sheath, is usually not difficult. Frequently, a nodularity in the tendon or definite crepitus can be felt as the finger is actively flexed. This may be accompanied by a locking of the nodule in the flexor sheath which requires passive extension in order to straighten the finger. Stenosing tenosynovitis in the thumb may present findings similar to those in the fingers but on occasion will present as a painful thumb, for which the cause is not obvious unless the comparative lack of motion of the interphalangeal and metacarpophalangeal joint is contrasted with the opposite side.

The etiology of the so-called stenosing tenosynovitis has been discussed from the point of view of a stenosis occurring in the tendon sheath, a combination of stenosis of the tendon sheath and thickening of the tendon, or a mechanistically induced, club-shaped swelling of the tendon where it receives pressure over the metacarpophalangeal joint during grasp. The trigger finger frequently occurs in more than one finger, and is often associated with de Quervain's disease and the carpal tunnel syndrome. In each of these conditions, one frequently finds hypertrophy and thickening of both the visceral and parietal layers of the tenosynovium and occasionally an actual inflammatory synovitis. The latter is more likely to occur in active rheumatoid arthritis, but may at times be a prodromal symptom of rheumatoid disease as well. The club-shaped swelling on the tendon at times may be peeled off as a part of the visceral tenosynovium. Often this tenosynovial hypertrophy invades the tendon fibers.

Numerous methods of treatment have been proposed for trigger finger, including the percutaneous slitting of the proximal pulley. In

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*See page 11.

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Warnings: Acute anaphylaxis (may prove fatal unless promptly controlled) is rare but more frequent in patients with previous penicillin sensitivity, bronchial asthma or other allergies. Resuscitative (epinephrine, aminophylline, pressor amines) and supportive (antihistamines, methylprednisolone sodium succinate) drugs should be readily available. Other rare hypersensitivity reactions include nephropathy, hemolytic anemia, leucopenia and thrombocytopenia. In suspected hypersensitivity, evaluation of renal and hematopoietic systems is recommended.
Precautions: In suspected staphylococcal infections, perform proper laboratory studies including sensitivity tests. If overgrowth of nonsusceptible organisms occurs (constant observation is essential), discontinue penicillin and take appropriate measures. Whenever allergic reactions occur, withdraw penicillin unless condition being treated is considered life threatening and amenable only to penicillin. Penicillin may delay or prevent appearance of primary syphilitic lesions. Gonorrhea patients suspected of concurrent syphilis should be tested serologically for at least 3 months. When lesions of primary syphilis are suspected, dark-field examination should precede use of penicillin. Treat beta-hemolytic streptococcal infections with full therapeutic dosage for at least 10 days to prevent rheumatic fever or glomerulonephritis. In staphylococcal infections, perform surgery as indicated.
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(potassium phenoxymethyl penicillin)

Wyeth

experienced hands this is undoubtedly a safe and effective method. However, the close association of the proper digital nerves and arteries and the possibility of producing an adhesion between the tendon sheath and the tendon from the use of a tenotome suggest that this procedure might be reserved for those who are also prepared to deal with the complications this method might induce. In many instances, a simple injection of ¼ ml of local anesthetic and 5 mg of a hydrocortisone preparation or its equivalent will give relief for weeks or months. This procedure is certainly fraught with less hazard. In a persistent or unimproved trigger finger, the slitting and removal of a section of the proximal pulley under local anesthesia and tourniquet control has much to recommend it. The tendons can be pulled individually from the tendon sheath and inspected, if done with a smooth blunt instrument so as to avoid adhesions. As has been recently pointed out by Flatt, some caution is advisable in suggesting surgical release, as the onset of a metacarpophalangeal synovitis may lead to the rapid production of ulnar drift due to the lack of restraint of the flexor tendon after its pulley has been excised, especially in the index finger.

Ronald L. Linscheid, M.D.
Rochester, Minnesota

Changes in the Skin with Internal Disease

IF ONE WERE asked what systemic disorders do not have a cutaneous component, much thought would be required to answer the question. Every increase or decrease in body temperature and almost any generalized stress reaction are associated with changes in the skin. However, pallor, sweating, and temperature variations occur in too many disorders to suggest a specific etiologic factor. Instead, they go along to support the correct diagnosis. Some cutaneous signs are of diagnostic importance. Fine telangiectasis at the base of the finger nails nearly always indicates a connective tissue disorder—lupus erythematosus, scleroderma or dermatomyositis. Jaundice points to hepatic disease, and blisters with residual scarring on the back of the hands, combined with a reddish hue, suggest porphyria. Numerous other examples can be given.

The same situation holds for internal cancer. A cutaneous change, such as pruritus or urticaria, may be the first indication of a neoplasm. Yet itching and hives appear so commonly in nonmalignant disorders that only in special situations would a physician consider cancer first to explain itching or hives. Other markers are more specific. Generalized herpes zoster or acanthosis nigricans occurring for the first time in an adult almost always results from internal cancer. The report by Perry, Kiely and Moertel* in the December issue of MINNESOTA MEDICINE describes six signs that may be associated with neoplasms. There are others, too, but the report is not intended to be an exhaustive review. The conditions listed, namely, plantar and palmar keratoses, generalized plane xanthomatosis, alopecia mucinosa, pemphigoid, multiple mucosal neuroma and ataxia-telangiectasis, although not common, are unusually interesting. The physician who grasps these entities has an expanded base for his diagnostic acumen.

Aaron B. Lerner, M.D.†
New Haven, Connecticut

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*Perry, Harold O.; Kiely, Joseph M., and Moertel, Charles G.: Cutaneous Clues to Visceral Cancer. Minnesota Med 51: 1719, 1968.

†Section of Dermatology, Department of Medicine, Yale University School of Medicine.

Conscience

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Tick-Borne Encephalitis

THE REPORT BY Spiess and Mumenthaler adds another country to the list of European countries in which tick-borne virus encephalitis has been recognized. In Europe, in contrast to the United States, ticks rather than mosquitoes are the important vectors of arboviruses that cause encephalitis. After severe encephalitis associated with tick bite was recognized in the eastern part of the U.S.S.R. during the 1930's, similar diseases were recognized in Czechoslovakia, Jugoslavia, Austria, Hungary, Bulgaria, Poland, Germany, Denmark, Sweden, Finland, and the British Isles. Two tick vectors are involved, *Ixodes persulcatus* in the eastern part of the U.S.S.R. and *Ixodes ricinus* in Europe. Three antigenically distinguishable, but closely related, viruses are the cause of tick-borne encephalitis, namely, Far Eastern in eastern U.S.S.R., Central European of Europe, and louping ill of the British Isles. The Far Eastern virus causes the most severe encephalitis. Generally, the disease is monophasic with signs of central nervous system involvement from the onset. Flaccid paralyses, particularly of muscles of the shoulder girdle, are common. The Central European virus usually causes a diphasic type of disease. A primary phase with influenza symptoms lasts about a week. Then, after an interval of several days when the patient feels better, a period of central nervous system involvement supervenes. Disease caused by these two viruses has also occurred after drinking raw goat's milk. Virus appears in the blood and is excreted in the milk of goats bitten by infected ticks. In the British Isles, louping ill virus is an important cause of encephalitis in sheep but only occasionally causes encephalitis in man, which resembles the Central European type.

Other members of this group of viruses cause febrile and hemorrhagic disease syndromes but not encephalitis. These are Omsk hemorrhagic fever virus of U.S.S.R. transmitted by *Dermacentor pictus* and Kyasanur Forest disease virus of Mysore State, India, transmitted by *Hemophysalis spingera*. In addition, there are members of this group of viruses which, because of their ecology, rarely come in contact with man: Langat virus of Malaya which is transmitted by *Ixodes granulatus* that apparently does not feed on man, and Powassan virus of Canada and the U. S. A. which is transmitted by *Ixodes* species that rarely if ever feed on man. Disease caused by Powassan virus has been established in only one patient, a boy who had onset of encephalitis in Powassan, Ontario, in 1958 and died. He may have been exposed by contact while hunting wild animals such as woodchucks, chipmunks, and wild mice that are involved in the infection chain that maintains the virus.

The only common tick-transmitted virus disease of man in the United States is Colorado tick fever, which occurs in the Rocky Mountain region within the geographic distribution of the spotted fever tick, *Dermacentor andersoni*. In this disease a diphasic illness resembling dengue, characterized by fever, severe general aching, and leukopenia is usually observed. Central nervous system involvement is rare. Colorado tick fever virus has not been isolated from ticks collected in Minnesota.

In the United States, four arboviruses have been recognized as a cause of encephalitis. These are Eastern (EEE) and western equine encephalitis (WEE), St. Louis encephalitis (SLE), and California encephalitis (CE) viruses. All of them are transmitted by mosquitoes. Three of them, WEE, SLE, and CE, have been recognized as a cause of encephalitis in Minnesota, usually in the period July to mid-September when enteroviruses, such as the Coxsackie and ECHO groups, may also cause meningitic and encephalitic syndromes.

Carl M. Eklund, M.D.†
Hamilton, Montana

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*See page 41.

†National Institute of Allergy and Infectious Diseases, Rocky Mountain Laboratory, Hamilton, Montana.

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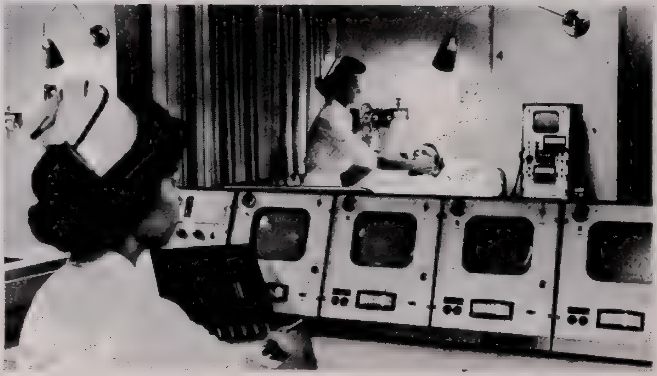

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Tetanus

Dr. Hans Stirnemann* extensively reviews the treatment of 217 cases of tetanus at the Surgical Clinic, University of Berne, Switzerland, during the fifty-year period 1918-1967. The disease is not common but must always be considered or proper diagnosis will not be made early, as shown in 35 "missed cases."

The intensive care of severe cases which includes tracheotomy, paralysis with curare, and respirator assistance has improved survival but has also caused complications and deaths. Tracheotomy may result in death from hemorrhage (two cases). Highly trained, motivated personnel are needed for prolonged patient support, including meticulous tracheotomy care. This study emphasizes the necessity to monitor and maintain normal blood gases and pH, avoiding the hyperventilation syndrome. The complications of stress ulcers are prevented by maintaining adequate nutrition and antacids via a small gastric tube.

We feel that high concentrations of oxygen for prolonged periods should be avoided because of potential pulmonary injury. The respirator lung syndrome is becoming more common.

Recent studies in this country have demonstrated rapid recall of antitoxin antibodies following the injection of 0.5 cc tetanus toxoid in individuals who were immunized over 10 years previously and had received no subsequent booster doses. Also, human tetanus antitoxin is now available, rarely causes any undesirable reaction and is therefore much safer than equine antitoxin (heterologous serum). Injured patients can be given a booster dose at the time of initial therapy, and individuals with grossly contaminated wounds or those having never been immunized should be given 400 units of human tetanus antitoxin in addition to the tetanus toxoid.

Both the laboratory and the clinical research has failed to demonstrate significant beneficial effects of hyperbaric oxygen in the treatment of tetanus in contrast to gas gangrene (Clostridium perfringens).

Tetanus is a continuing problem in the industrial-agricultural communities and carries a significant mortality if unrecognized or inadequately treated. Fortunately tetanus, although difficult to treat, can be completely prevented by the continuing education of the public and by active immunization.

R. Duncan Sutherland, M.D.
John J. Haglin, M.D.
Minneapolis, Minnesota

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*See page 15.

Milk: Indications and Contraindications

It is a bad thing to give milk to persons having headache, and it is also bad to give it in fevers, and to persons whose hypochondria are swelled up, and troubled with borborygmi, and to thirsty persons; it is bad also, when given to those who have bilious discharges in acute fevers, and to those who have copious discharges of blood; but it is suitable in phthisical cases, when not attended with very much fever; it is also to be given in fevers of a chronic and weak nature, when none of the aforementioned symptoms are present, and the patients are excessively emaciated.*

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*Hippocrates

Enough of a great physician's experience dies with him to justify the saying, "There is no wisdom in the grave."

Put off your imagination, as you put off your overcoat, when you enter the laboratory. But put it on again, as you put on your overcoat, when you leave. Claude Bernard

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Renal Clearances

THE APPEARANCE of ^{51}Cr-EDTA as an estimate of glomerular filtration rate constitutes another useful item in the armamentarium of the diagnostician of renal diseases.

The use of ^{51}Cr-EDTA would appear rather limited, however, because its correlation with standard materials used to estimate glomerular filtration rate, such as inulin, is less than that of other radioactive compounds which are more convenient to use, such as diatrizoate (Hypaque). Moreover, Hypaque labelled with ^{125}I or ^{131}I is available, and this provides great flexibility in usage because these two isotopes may be quantitated individually in mixture. Such quantitation would allow, for example, glomerular filtration rate and effective renal plasma flow to be measured simultaneously. Diatrizoate-^{125}I could be used to measure glomerular filtration rate, and *o*-iodohippurate-^{131}I to estimate effective renal plasma flow. The latter compound labelled with ^{125}I is also available. In addition, these compounds yield clearance estimates that correlate well with glomerular filtration rate and effective renal plasma flow when single injection methods are used, provided the proper compartment model is chosen. Apparently, ^{51}Cr-EDTA cannot be so used, according to the accompanying paper. Nor can ^{51}Cr and ^{131}I be easily quantitated individually in mixture.

Despite these shortcomings, ^{51}Cr-EDTA may have a place in the renal physiology laboratory. Estimates of glomerular filtration rate may be desirable when radioiodine-labelled compounds cannot be used or when sequential studies using multiple labels are to be done. Thus, any new compound that estimates glomerular filtration rate is welcome.

W. Newlon Tauxe, M.D.
Rochester, Minnesota

See page 37.

Test Your Word Score

Alphanumerical—*Consisting of both letters and numbers* (page 70).

Vector—*a carrier* (page 42).

Poisson distribution—*Simion and Poisson,* 1840 (page 54).

Iron kinetics—*the metabolism of iron* (page 47).

Clavus—*corn; a small callosity caused by pressure* (page 13).

Listeriosis—*infection caused by organisms of the genus Listeria* (page 128).

Dysplastic—*having abnormal tissue development* (page 157).

Diaphanoscope—*an instrument for illuminating a body cavity* (page 109).

Antigenic—*having property of stimulating formation of antibodies* (page 137).

Covalent—*a nonionic chemical bond* (page 143).

Restitutio ad integrum—*complete return to health* (page 20).

Eluted—*washed out* (page 176).

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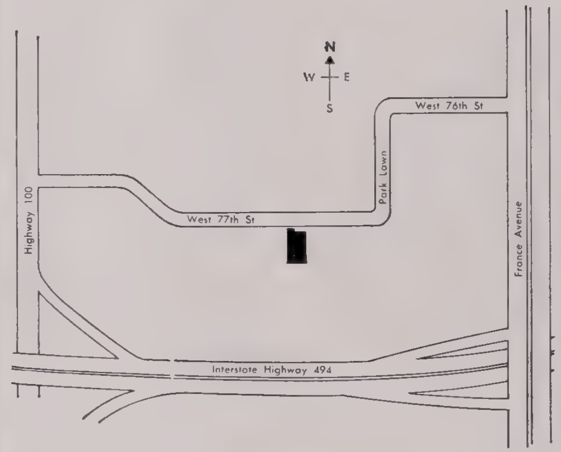
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The Editor's Soliloquy

The Span of a Professional Lifetime

YEARS AGO YOUR Editor studied for the better part of a year at the University of Berne under the tutelage of Professor de Quervain to learn the intricacies of goiter disease. I was classified as an Austausch assistant. Accompanying me to Switzerland were my wife and two infant daughters.

Having passed the required German tests for a graduate degree, I assumed that my diligence in studying the German language while speaking to Swiss students would make my accent acceptable. For the first few weeks, however, I had difficulty adjusting my ear to the slow, throaty but tuneful C sound of the Berne-Deutsch articulation. In an effort to improve my pronunciation after listening to the medical students converse with one another, I read aloud the medical literature of the Swiss journal. A year later in Minneapolis, when I called to converse with a German who was having difficulty with English, he asked me, to my surprise and delight, where I had picked up my authentic Berne-Deutsch accent which was almost as foreign to him as the English language.

Berne, Switzerland, keystone to the surrounding mountain regions, is one of the most unique and beautiful cities of Europe, its "old-town" section lying snugly within a bend of the river Aare. Its main street, extending from the Inselspital (Island Hospital) to the Barengraben (Bear pits), has retained its original architecture for almost a thousand years; but other portions of the city, the "new-town" areas, have developed with the times and are as modern as the main street is medieval. This harmonious juxtaposition of "new" and "old" furnishes concrete evidence of Berne's historical continuity (from the 12th to the 20th century) and constitutes one facet of its charm.

Tradition has it that in 1191 patrician founders of the community went hunting and sportingly agreed to name the new settlement after the first animal they shot, which turned out to be a bear. The Old High German Bero still adorns the city seal, and the Barengraben has been one of Berne's distinctive attractions throughout the centuries. Among the city's other unique features are picturesque streets and houses of medieval vintage, enticing promenades, terraces and arcades, and especially fountains: the Bagpiper, the Standard Bearer, the Marksman, and the Ogre—each unit either historically or culturally significant.

The pervasive medieval aura of the city is most manifest in its remnants of ancient walls that retain two of their original towers: the Kafigturm (prison tower) and the Zeitglockenturm (clock tower) with its elaborate ritual of striking the hour.

Perhaps even more memorable than its scenic and cultural attractions is Berne's intangible quality of "Gemutlichkeit," one of those happy German composites, the apt grace of which is untranslatable into harsher Anglo-Saxon. Somewhat similar to the French "joie de vivre," Gemutlichkeit consists of cheeriness, kindliness, cordiality, and courtesy, all warmly blended and delivered with that "light touch" so alien to most northern cultures.

Professor de Quervain was an exceedingly energetic and gracious person, deeply religious and possessed of a high degree of intellectual integrity. In addition to several Swiss dialects he spoke five languages fluently. While

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PUBLISHED AS A PUBLIC SERVICE IN COOPERATION WITH THE being entertained at his lovely home with the other students in his department, I once asked him which of the many languages he preferred. Without hesitation he pronounced the Berne-Deutsch to be the most beautiful of all. It was a delight to watch him converse with his retinue of foreign visitors, each in their own language, shifting from one to the other with facility and obvious inner satisfaction. He loved a well-turned anecdote and was especially fond of the story about an English woman who pointed to one of the dwarfed cretins and remarked, "There is a typical Berne Deutscher!"

Among his students was a charming young intellectual, ever gracious and considerate to associates. A keen, eager student in most phases of medical science, he demonstrated an interest in research which led him into many phases of medical investigation in addition to his chosen field of surgery. Incidentally, he often spoke of the disadvantages of extreme specialization.

As counterbalance for the arduous mental discipline of academic and scientific pursuits this young man strongly advocated the equally strenuous Swiss sports: mountain climbing and skiing.

The name of this fellow student was Karl Lenggenhager.

Timidified by my lack of ability to converse well in their language, Karl always gave me confidence and courage when I needed it most. Perhaps because of our first names I felt a common bond: his spelled with a "K," mine with a "C." Besides encouragement he often gave me valuable tips for weekend visits throughout Switzerland—to various points of historical, national, or scenic interest.

Ten years later, in 1940, Dr. Karl Lenggenhager was appointed Chief of Surgery to succeed Professor de Quervain. One of his major interests in research pertained to the coagulation of blood and the genesis and prevention of pulmonary embolism, for which he introduced postoperative prophylaxis with heparin. He has also published numerous technical improvements in a wide field of surgery.

Professor Lenggenhager has always been a gentleman to his fingertips. By nature a modest and kindly man he has not sought fame or power for himself, but has delegated responsibilities to his associates, trusting them and supporting their theories and projects, and judiciously settling differences of opinion within his department and among the faculty.

It is through my good fortune in having known this man that a Special Issue of MINNESOTA MEDICINE has been made possible; it represents almost the span of a professional lifetime.

Carl O. Rice, M.D.

Old Doc Hess Says: Do only what is right and quit counting noses. C.O.R.

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Keep your eyes wide open before marriage, and half-shut afterwards.—Benjamin Franklin

My Political Creed

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For I believe that the values upon which this country was founded are immutable and have not been eroded by the passage of years.

I believe that I, as a free citizen in a free land, am obligated to defend my beliefs in the ways permitted to me, and required of me, by our form of government.

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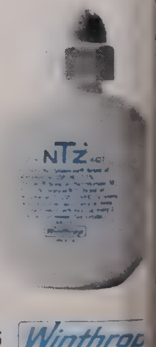

Curbstone Consultation

QUESTION: Occasionally the PBI and T-3 results don't jibe in women on oral contraceptives. How should we approach thyroid function in women on hormones?

ANSWER: First a few scraps of important information: (1) Most thyroxine binds to globulin in serum; less than 0.1% goes unbound, or "free." (2) PBI measures mostly the iodine attached to this globulin. (3) The amount of globulin inversely affects the T-3 value (the more globulin circulating, the less radioactive tri-iodo-thyronine "taken up"). When a woman takes birth-control pills, estrogen in the pills increases that portion of protein to which thyroxine clings, thereby forcing the PBI up and the T-3 down.

We recently went over the drug histories of 50 women on contraceptive pills who had high PBIs and low T-3s. Types of pills included C-Quens, Enovid and Enovid-E, Norinyl and Norinyl-1, Ortho-Novum, Ovulen, and Provest. Thus, all the commonly used agents exerted a thyroid effect. And a significant one, too. Values for PBI ran from 8.1 mcg.% to 21.0 mcg.% (mean 10.1 mcg.%) and for T-3 from 24% to 8% (mean 19%).

Yet when we multiplied PBI by T-3 to get a Free Thyroid Index:

PBI	×	T-3	=	FTI
(4–8 mcg.%)		(25–35%)		(100–280)

48 patients fell into the euthyroid range. From this and other studies, we are convinced the Index reliably measures thyroid status when patients have drug or disease-induced protein charges.

Up to this point we have not mentioned two other serum tests: T-4 by column chromatography and "free" T-4 by a mixed isotope dilution method. In our hands, the T-4 column test, though accurate and precise enough, has not solved the pill problem. Like PBI, estrogen sends it up. And, like PBI, drugs containing organic or inorganic iodine cause high results. Theoretically, "free" T-4 ought to be the answer since globulin changes do not influence it. But it is more expensive than a PBI and T-3 together, gives about the same information[1] and, at least in the Mayo Clinic experience, "distinguished poorly between different levels of thyroid function."[2]

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Men are not punished for their sins, but by them.—E. Hubbard

New drugs take exams, too.

Today, virtually every medical school in the United States cooperates with pharmaceutical manufacturers in the clinical evaluation of new and promising drugs. Just as you might find it significantly more difficult to practice medicine without the useful new compounds made available through original pharmaceutical research in the past twenty years—prescription-drug manufacturers would find it equally difficult to obtain extensive, long-term, dependable evaluations of new therapeutic agents without the close cooperation of medical staffs and clinical facilities of medical schools and teaching hospitals. Such cooperation leads toward more effective care of more patients—the common goal of medical and pharmaceutical research—toward reduction in the cost of disease, toward increase in useful longevity.

This message is brought to you as a courtesy of this publication on behalf of the producers of prescription drugs.

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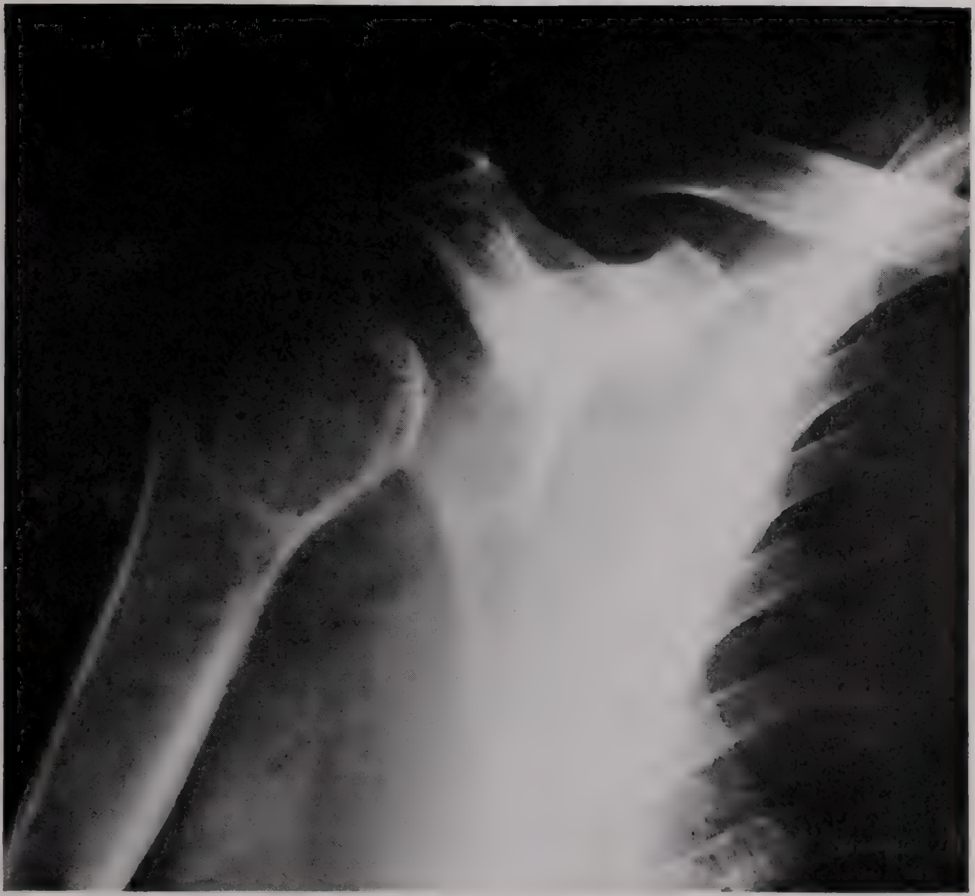
The Viewing Box

Shoulder Pain

THIS 58-YEAR-OLD MALE fell and hit his right shoulder. He complained of pain in the shoulder. Clinically the shoulder motion was limited. Roentgenograms were obtained. The anteroposterior view is shown here (Figure).

What is your diagnosis? (See next page).



Figure

Diagnosis: Posterior dislocation of right shoulder.

This case is presented because at least one half of the posterior shoulder dislocations are either missed or misdiagnosed.

The frequency with which this diagnosis is missed is largely the result of four factors: (1) the injury is rare, accounting for only 2 to 4% of all shoulder dislocations; (2) the anteroposterior roentgenogram may be deceptively normal; (3) The clinical findings are often subtle; (4) symptoms of the dislocation may be attributed to associated fractures.

Approximately one half of the cases result from convulsive episodes. The remainder are produced by a direct blow to the anterior surface of the humeral head or a force transmitted along a flexed, adducted and internally rotated humerus. The displaced articular surface of the humeral head comes to rest behind the glenoid, facing posteriorly with the humerus locked in internal rotation. The soft anterior surface of the anatomic neck hinges on the hard posterior rim of the glenoid. A deep notch in the humeral head may result. This will obliterate the second diagnostic feature to be discussed.

The following roentgen findings may be useful in the diagnosis of posterior shoulder dislocation: (1) "positive rim sign": an increase in space between the anterior rim of the glenoid and the medial aspect of the humeral head. In the normal adult shoulder this distance does not exceed 6 mm regardless of rotation or projection (36-40 inch target to film distance); (2) absence of half-moon overlap. Normally, the medial part of the head of the humerus overlaps the glenoid to form an elliptical (half-moon) shadow; (3) internal rotation; (4) associated fractures of the humeral head.

This patient exhibited the following typical radiographic findings: (1) positive rim sign (23 mm); (2) absence of the half-moon overlap; and (3) internal rotation. There is no fracture. A transthoracic lateral view (not reproduced) confirmed a posterior dislocation.

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On Dropsies

All dropsies arising from acute diseases are bad; for they do not remove the fever, and are very painful and fatal. The most of them commence from the flanks and loins, but some from the liver; in those which derive their origin from the flanks and loins the feet swell, protracted diarrhoeas supervene, which neither remove the pains in the flanks and loins, nor soften the belly; but in dropsies which are connected with the liver there is a tickling cough, with scarcely any perceptible expectoration, and the feet swell; there are no evacuations from the bowels, unless such as are hard and forced; and there are swellings about the belly, sometimes on the one side and sometimes on the other, and these increase and diminish by turns.*

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*Hippocrates: The Book of Prognostics

The surest way to corrupt a young man is to teach him to esteem more highly those who think alike than those who think differently.—Nietzsche

Dermatology

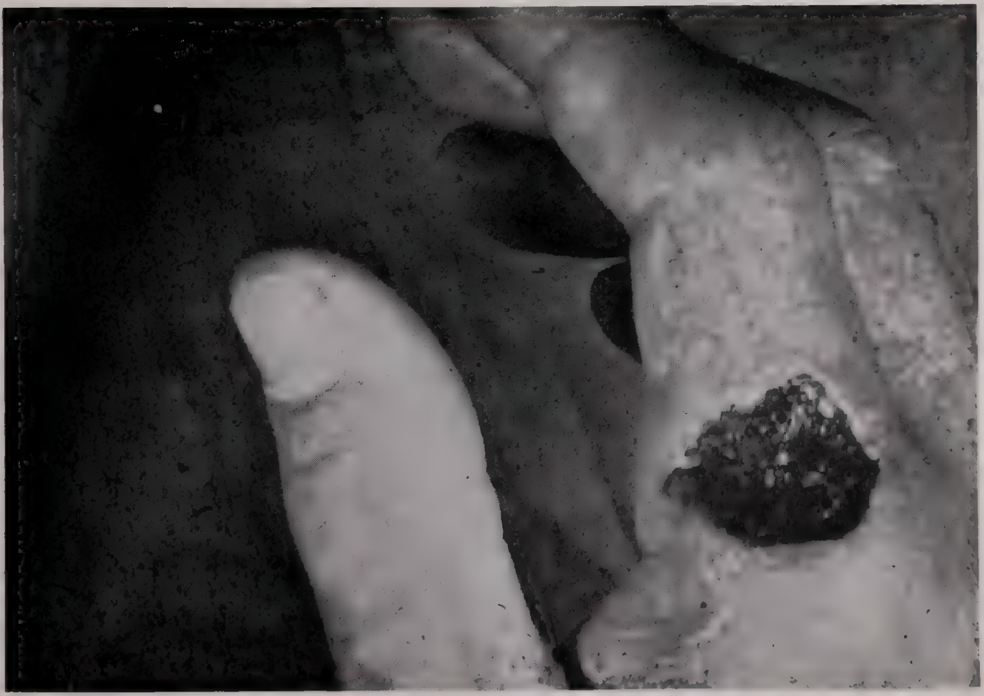
Self-Induced Eruptions

SELF-INDUCED CUTANEOUS damage varies from simple excoriations to severe and disfiguring mutilations. Generally, self-induced eruptions may be divided into two groups: neurotic excoriations and factitial dermatitis. Both are characterized by underlying emotional disturbances and refractoriness to treatment. A major point of differentiation is that the patient with neurotic excoriations will admit that he damages his skin, while in factitial dermatitis the patient denies any responsibility for the damage and may not consciously admit it even to himself.

It is generally agreed that persons who seriously damage themselves are deeply disturbed. This disturbance may range from mild neurosis to severe psychosis. Some consider these individuals as being basically hysterical, but conversion hysteria does not characteristically include self-injury or mutilation. It may be that self-inflicted damage results from guilt or aggressive feelings turned back upon the individual, with conscious satisfaction resulting from the self-injury.

Neurotic Excoriations

This heading covers patients who aggravate an existing dermatosis and also those who actually create an eruption or damage. Aggravation of dermatoses is frequently seen in acne vulgaris and in atopic or neurodermatitis.



Figure

These patients are usually of the anxious-obsessional personality type. In acne the patient may pick at his face until permanent scarring results.

Neurotic excoriations are more severe; as a rule there is no primary dermatologic disease preceding the self-inflicted damage. It must be pointed out that simple aggravation of a dermatosis and frank neurotic excoriations are not always easily separated.

Lesions of a neurotic excoriator are frequently characteristic. They occur on those areas the individual can easily reach (face, shoulders, chest, forearms, and anterior thighs). The patient usually feels there is a "core," "pimple," foreign body, or other irregularity in the skin which must be removed. At times only a diffuse itching is described. His actions are compulsive and apparently result in relief of his tension. The lesions themselves are often linear or irregular, may be superficial or deep, are usually covered by a crust or scab, and have an erythematous border. When the lesion heals there is a scar surrounded by an area of hyperpigmentation.

If an attempt is made to stop the patient's activities, tension builds up to an intolerable level (unless he is given a harmless substitute such as a lotion to apply) and resumption of the destructive behavior ensues.

Factitial Dermatitis

In this condition the patient consciously produces the lesions but will deny that he has done so. This disease usually is indicative of a severe neurosis or even an underlying psychosis. The diagnosis of factitial dermatitis is based upon location of the lesion, its clean-cut and bizarre appearance as well as the exclusion of any recognizable dermatologic diseases which might cause such changes. The artificial appearance arouses suspicion (Figure). Patients may use chemicals, heat, instruments, and nails or teeth in producing the damage. As a result the lesions usually have a distinctive appearance not seen in naturally occurring dermatoses.

Primary in this dermatosis is the patient's denial of his responsibility in producing the damage. The location as a rule is on those areas where the lesion may attract attention for sympathy, pity or monetary compensation, or where it can be used for escaping responsibility. Many of these patients are middle-aged and may have various feelings of inadequacy. This inadequacy may be real or imagined; nevertheless, the patient cannot accept it and uses this mechanism to rationalize his failure to achieve.

Treatment

In both these conditions dermatologic treatment is directed towards the induced lesions with ointments and protective or occlusive dressings to prevent further damage. At times in neurotic excoriations, superficial physchotherapy has been reported to be beneficial. However, in factitial dermatitis many observers feel these patients are often of a low intellectual level where psychiatric help even if available rarely helps. Regardless, it is considered unwise in this latter condition to uncover the patient's self-destructive behavior without psychological evaluation so that treatment may proceed with psychiatric guidance.

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To my embarrassment I was born in bed with a lady.—Wilson Mizner

Tumor Conference

Diagnosis and Treatment of Malignant Testicular Tumors

THE FREQUENCY of malignant tumors of the testes is 0.5-2% of all malignancies in males and up to 4% of all malignant tumors in the male urogenital tract.[1,2] Early diagnosis significantly improves therapeutic results and thereby the prognosis and life expectancy of patients with this malignant disease which involves particularly young persons. Based upon the following case history some problems of diagnosis and treatment of testicular malignancies are discussed.

Case History

A 32-year-old engineer observed a hard swelling of his right testicle for the first time in July 1964. Four months later he consulted his physician, who advised surgical excision because he could not differentiate clinically between a growth originating from the testicle and the epididymis. At surgical exploration the tumor was clearly confined to the testis.

Pathologic Findings

Microscopically no infiltration of the epididymis and the deferent duct was observed. The histological diagnosis was embryonal carcinoma; lymphography performed 14 days after the operation did not reveal metastases in the aortic and iliac lymph nodes (Figure 1). Contrast filling of the aortic node groups was observed up to the region of L2. Some lymph nodes situated parallel to the thoracic duct at the level of Th 10/12 and Th 6/7 were also filled with contrast agent. In this region the thoracic duct was duplicated and tortuous (Figure 2). No metastases in the lungs were detectable. The gonadotropins in the urine were normal. Prophylactic radiotherapeutic treatment was performed with Co^{60}; 3234 rad were applied to the inguinal and iliac node groups on a 19 x 9 cm portal in 36 days and 3466 rh inguinal-iliac on a 16 x 9 cm umbilical portal. The usual irradiation dose of 4500 rh could not be given in both areas because of increased skin reaction. At the end of the treatment no metastases in the lungs and contrast-filled lymph nodes were observed.

Progress

Five months later a solitary metastasis in the right upper lobe of the lung was present, which increased rapidly in size during the next two weeks. Chemotherapy with an initial dose of 50 mg methylhydrazine was started on July 25, 1965. Combined radiotherapy and chemotherapy was given in 14 sessions over a period of 18 days; 250

mg of methylhydrazine was injected after each irradiation up to a total dose of 3.05 g. The lung metastasis was irradiated with high-speed electrons alternately from a 7 x 7 cm ventral and dorsal portal with a total dose of 2810 rad. On radiographic controls the lung metastasis gradually disappeared and was not detectable at the end of the combined treatment. For the next 20 months the patient did not present any abnormalities.

On April 12, 1967, he complained for the first time about substernal pain, but no pathological findings in the lungs were detected. About three months later he consulted his physician because of fever, cough and massive sputum. Fluoroscopy demonstrated pneumonic infiltration of the right middle lobe. Therapy with achromycin led to rapid clinical improvement. A subsequent radiographic control of the lungs revealed an expansivity of the right posterior hilar region at the site of the lymph nodes filled with contrast medium at the previous lymphography (Th 5-7). Oblique tomography demonstrated a moderate concentric stenosis of the right stem bronchus due to enlarged hilar and posterior mediastinal lymph nodes (Figure 3), a finding which was

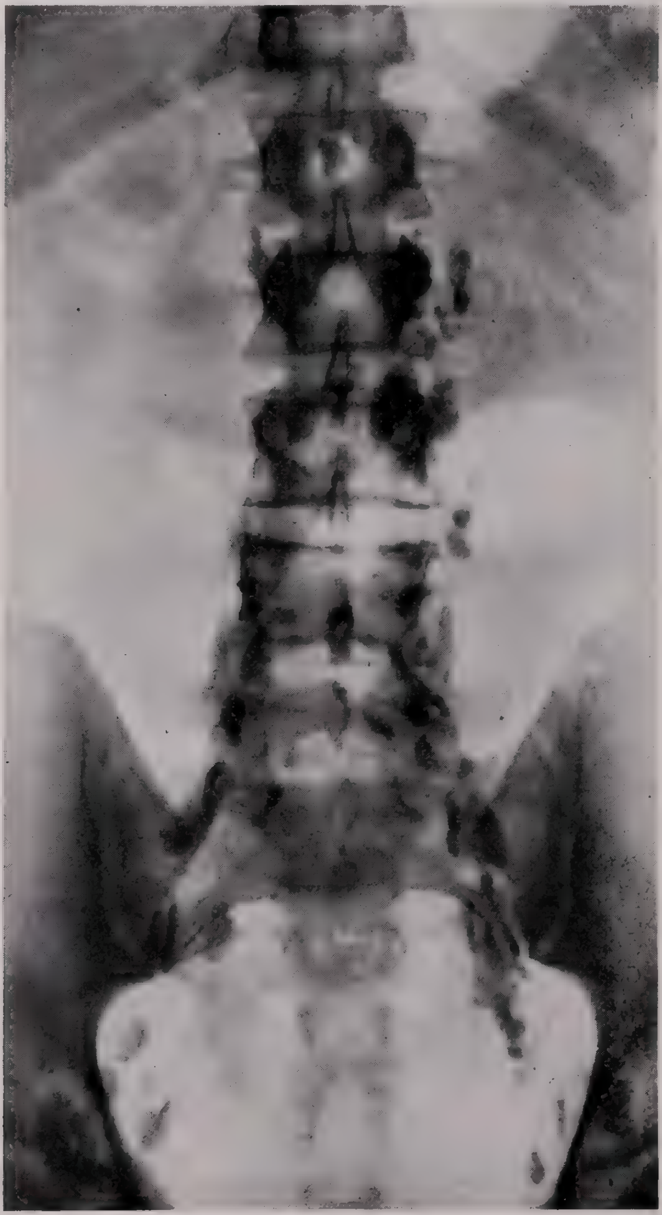

Fig. 1—Normal lymphogram of the aortic and iliac lymph nodes.

confirmed by bronchoscopy five days later. On August 31 the patient was taken to the hospital and therapeutic treatment with high-speed electrons to the mediastinal region was initiated.

Unfortunately treatment had to be interrupted on September 9 after administration of only 1240 rad, because a fistula at the level of the tracheal bifurcation between the posterior mediastinum and the esophagus had rapidly developed (Figure 4). Septic temperature was present and the general state of the patient was poor. Radiologically a mediastino-costo-diaphragmatic pleural lesion had developed on the right side of the lower posterior mediastinum.

Lymphography, cavography and urography performed after moderate recovery of the patient due to treatment with antibiotics did not show metastases within the retroperitoneal region, a finding which was confirmed at laparatomy for gastrostomy. The lymph nodes at Th 6/7 were enlarged but not contrast-filled because of complete malignant infiltration. Occlusion of the anterior branch of the thoracic duct and slight dislocation of the posterior branch were present (Figure 5).

On October 3 the esophago-mediastinal fistula was clinically closed. Roentgen-examination of the chest showed no change of the costo-diaphragmatic pleural lesion,

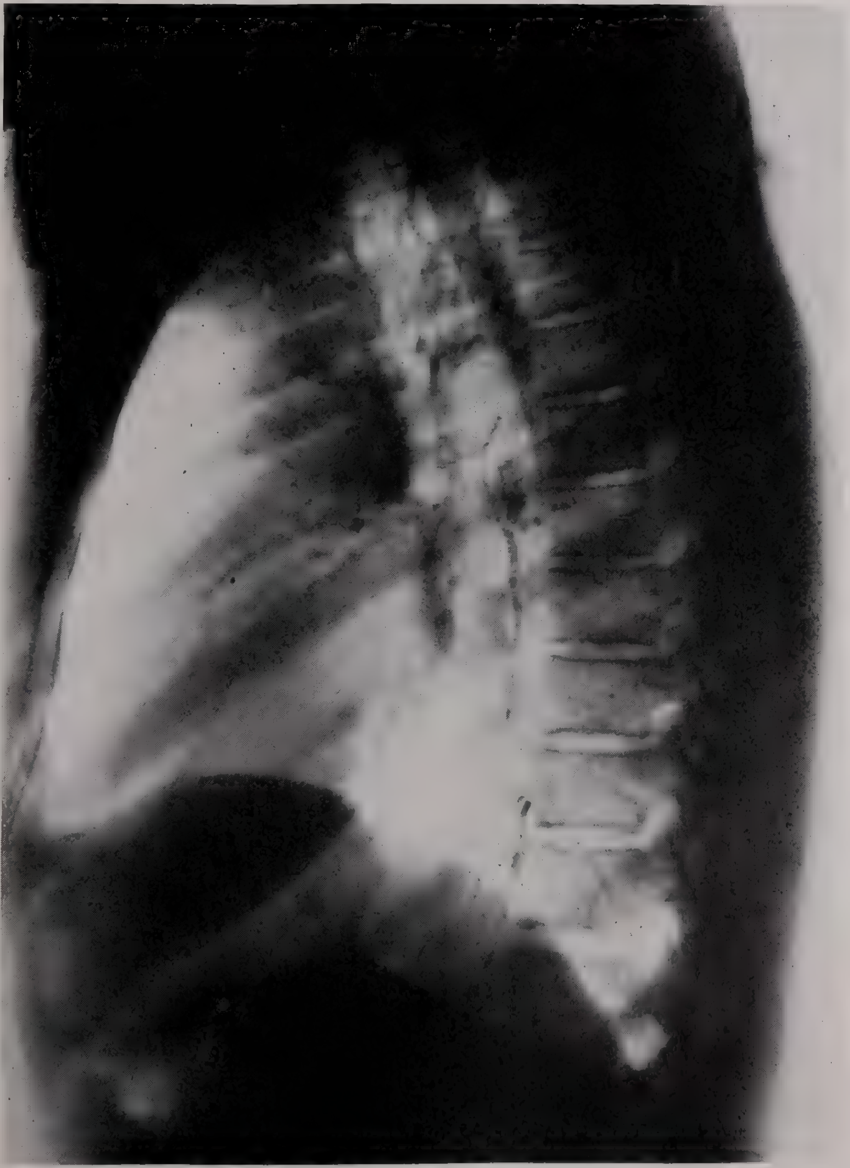

Fig. 2—Duplication and tortuosity of the thoracic duct of Th 5/7. Contrast-filled lymph nodes at the level of Th 6/7 (→) and Th 10/12 (→).

but chronic pneumonia of the right lower lobe and metastases in the left upper lobe were suspected. A first attempt to drain the mediastinal abscess was unsuccessful. As the septic condition persisted, a second drainage of the abscess was performed which resulted in an improvement in the clinical condition of the patient. The gastrostomy was then closed and the patient showed further improvement; but 20 days later acute respiratory insufficiency due to tracheal compression developed. Emergency bronchoscopy revealed complete occlusion of the right and subtotal stenosis of the left main bronchi. Removal of the occlusive tumor masses within the left main bronchus by electrocauterization slightly improved the respiratory function; but on the following day emergency bronchoscopy was again necessary and the patient died of acute respiratory failure.

The Postmortem Study

Metastases of an embryonal carcinoma with inclusion of cellular formations similar to a chorio-epithelioma in the region of the right main bronchus. Partial tumor necrosis and perforation into the bronchi, trachea and esophagus. Esophago-mediastinal fistula, 4 cm in diameter. Metastases in both lungs and pleural cavities. Posterior mediastino-costo-diaphragmatic abscess on the right side.

Diagnostic Studies

Clinical diagnosis of testicular tumors is relatively easy. A hard swelling of the testicle in a male between 20 and 50 years, producing no other symp-

Fig. 3—Concentric stenosis of the right stem bronchus (→) due to the enlarged hilar and posterior mediastinal lymph nodes.

toms, must be considered highly suspicious for malignancy. Inflammatory swellings of the epididymis are generally painful. Hydrocele of the testis can be ruled out by palpation and diaphanoscopy.*

Orchidectomy usually confirms the clinical diagnosis of malignancy. In cases where surgical exploration does not give a conclusive diagnosis, biopsy of the tumorous mass is indicated.

Histological Classification

Malignant testicular tumors comprise two categories: the germinal (96.5%) and non-germinal groups (3.5%). The germinal group included the following tumors:

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*See Test Your Word Score Page 89.

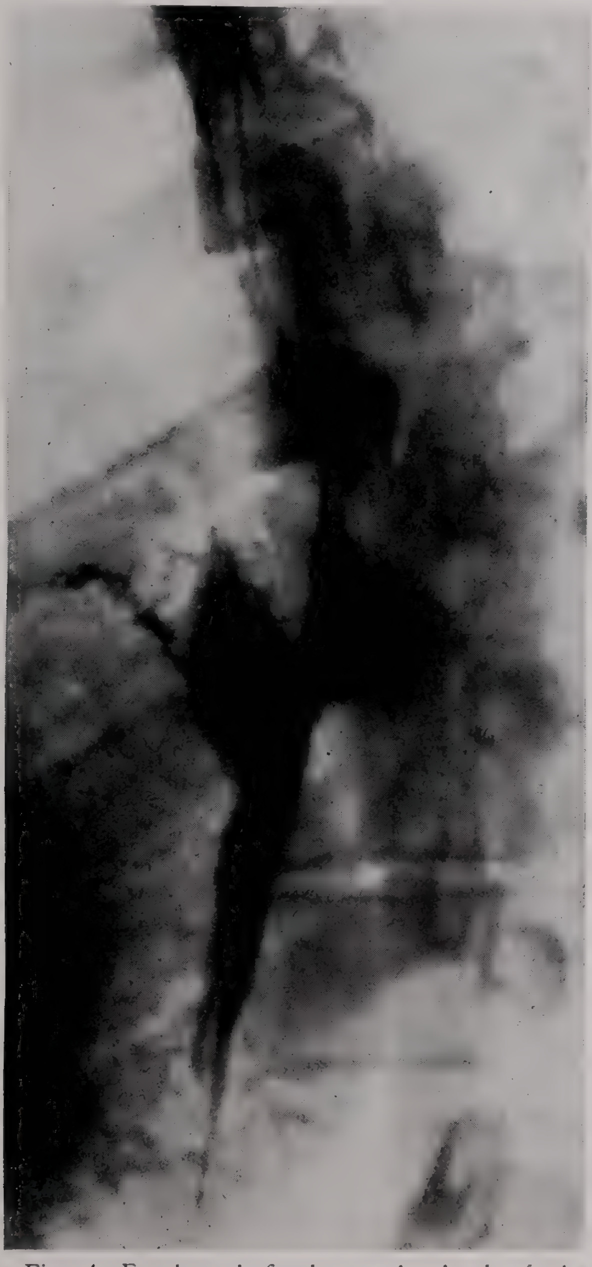

Fig. 4—Esophageal fistula at the level of the tracheal bifurcation due to malignant infiltration arising from the lymph node metastases.

Seminoma is the largest group with a relative frequency of 40%. It is the least malignant, the most radiosensitive, and the most radiocurable tumor of the testis.

Embryonal carcinoma (25%) has a consistent, highly malignant clinical behavior and shows a variety of histological pictures.

Teratoma (30%) is made up of recognizable somatic tissues corresponding to either fetal or adult stages of development. Teratoma is very often associated with either embryonal carcinoma, choriocarcinoma or both, and is then called *teratocarcinoma* (20%), the clinical behavior of which is dominated by the trophoblastic component.

Choriocarcinoma is the most malignant variety.

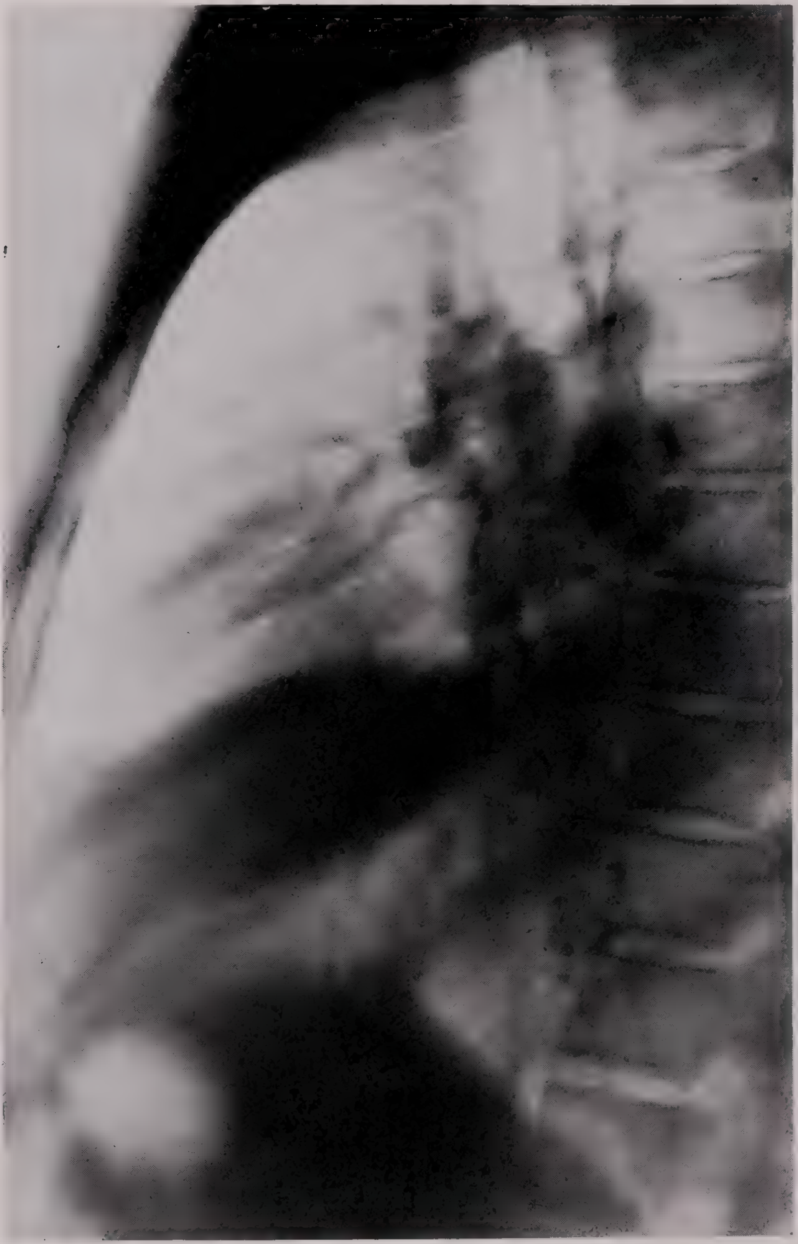

Fig. 5—Tumor metastases within the mediastinal lymph nodes at the level of Th 6/7 (→). Obstruction of the anterior branch and slight dislocation of the posterior branch of the thoracic duct.

Roentgen Studies

Evaluation of the lymphatic *metastatic spread* is important to judge therapy and prognosis. Roentgen examination of the lungs, lymphography, cavography and urography are necessary to detect clinically metastatic involvement or regional lymph nodes.

The *anatomy of the regional lymph nodes* is characterized by the fact that four to eight efferent lymph channels of the testis drain directly into aortic lymph nodes situated distal to the renal blood vessels. The lymph vessels of the right testis drain into the right latero-aortic and preaortic lymph nodes, those of the left testis into the left latero-aortic and preaortic lymph nodes. A few lymphatics arising from the medial aspect of the testis and the epididymis are closely connected with the deferent duct and enter the external iliac lymph nodes.[5]

Lymphography by injecting oily contrast material into a subcutaneous lymphatic of the foot does not visualize all the first regional lymph channels of the testicle. By injection of contrast medium directly in the efferent lymphatics of the testis during orchidectomy, one or several lymph nodes are filled at the level of the first to second lumbar vertebrae on the left side and of the first to the third lumbar vertebrae on the right side.[4,15] These lymph nodes are situated laterally to the aortic lymph nodes outlined by foot lymphography and are only occasionally demonstrated by the conventional method. Consequently neither foot nor testicular lymphography gives a complete visualization of the regional lymph nodes of the testis. Combined studies could give optimal results, but testicular lymphography is too tedious for routine use. False negative findings are therefore possible in conventional lymphography.

According to anatomical dissection studies the right latero-aortic node group contains far more nodes than the other aortic chains. Analyzing the aortic lymph node groups in 100 normal lymphograms,[12] the number of nodes demonstrated in the right aortic node groups is two to 18 with an average number of eight and is therefore by far the smallest compared to 12 of the pre- and retroaortic groups and 16 of the left latero-aortic group. In 40% of all cases the upper level of the right latero-aortic nodes filled with contrast agent was situated at L 3, and only in 10% at L 1. The classical finding of three equally developed aortic lymph node chains is therefore present in only about 25% of all cases and scarce visualization of the right aortic node group in the lymphogram is relatively common. Cavography as an additional method will reveal metastases to this node group by indirect roentgendiagnostic signs, such as compression, dislocation and infiltration.

Lymphographic Diagnosis

Lymphographic investigations of patients with malignant tumors of the testis have been reported.[2,10,13,16,18]

Seventy-four patients with malignant testicular tumors were investigated by mainly bilateral foot lymphography after unilateral orchidectomy and prior to radiotherapy. No testicular lymphograms were done. Thirty-six cases were seminoma, 16 embryonal carcinoma, 11 teratocarcinoma, four teratoma, two choriocarcinoma and five non-germinal malignant tumors. Thirty-four patients (46%) showed pathological lymphographic findings. The rate of malignant metastatic spread to regional lymph nodes was approximately 50% in embryonal carcinoma, teratoma, teratocarcinoma and choriocarcinoma, whereas one third of the seminoma group had lymph node metastases.

The high diagnostic value of lymphography for detecting malignant metastatic spread becomes evident when comparing the figures in a series of 900 cases not investigated by lymphography.[7] The incidence of lymph node metastases was 11% in seminoma, 24% in teratoma, and 30% in embryonal carcinoma and teratocarcinoma. In our case material bilateral metastases in the regional aortic lymph nodes were found in 11 patients and unilateral metastases on the contralateral side in two patients. Malignant spread to the iliac node groups was demonstrated in 10 advanced cases, five of which showed bilateral involvement. Only one patient with malignant infiltration of the scrotum had evidence of inguinal lymph node metastases.

Inguinal metastases can also be due to a reflux of tumor cells from the iliac region. Enlarged lymph nodes with filling defects were present in 31 cases and dislocation of lymph nodes and lymph vessels in 14 cases. Stasis of the lymphatic circulation was observed in 13 patients and non-filling of node groups due to malignant infiltration, leading to a collateral circulation, in six cases. Obstruction of the thoracic duct occurred occasionally.

Different histological types of malignant testicular tumors lead to identical lymphographic findings. Filling defects in lymph nodes due to metastatic deposits and slight dislocation of the normal contrast-filled lymphatic tissue are found in early forms of metastases. Extensive displacement of the remaining lymphatic tissue, complete replacement by malignant tissue, and blockage of the lymphatic circulation indicate advanced stages of malignant disease. Diagnosis of metastases in aortic lymph nodes at the level of the kidneys may be difficult because reactive hyperplasia of this group of nodes is a common finding. Reactive hyperplasia indicates a response of the lymph nodes to agents such as tumor cells or unspecific or inflammatory toxic agents especially after orchidectomy. Follow-up studies and second-look lymphograms of these lymph nodes are necessary to detect metastatic involvement at a later stage.

Accurate staging, exact planning, and control of treatment are the clinical indications for performing lymphography in cases of *seminoma*. Preoperative localization of lymph node metastases is of great importance in *teratocarcinoma* because excision of the aortic lymph nodes in unilateral metastases gives good results. Preoperative radiographic control facilitates the complete operative removal of the regional lymph nodes infiltrated by tumor. In cases of *choriocarcinoma* lymphography may give information about prognosis and therapy results in spite of the poor prognosis of these malignant tumors.

Treatment Techniques

Orchidectomy

Treatment of testis tumors entails *radical orchidectomy* as the first measure. According to the histological type of the malignancy and the extent of metastasis, different treatment techniques are employed.

Irradiation

In *seminoma* prophylactic and therapeutic irradiation of the retroperitoneal lymph nodes is given on an iliac (right or left) and an umbilical portal; both the inguino-iliac and aortic node groups are irradiated with a total dose of 4000 rh Co^{60}. In cases of positive lymphographic findings in the aortic lymph nodes additional prophylactic regional irradiation of the left supraclavicular lymph node groups with 4000 rh caes is performed. Cases of *embryonal carcinoma,* including *choriocarcinoma* and *teratocarcinoma,* are prophylactically and therapeutically irradiated with a total dose of 4500-5000 rh Co^{60} in both the inguino-iliac and aortic regions. Prophylactic irradiation[9] of the left supraclavicular region with a dose of 4000 rh caes is routinely given.

Prophylactic irradiation treatment of the supraclavicular node groups should, however, be guided to a greater extent by the results of lymphography. In a study of 336 lymphograms of our case material[11] contrast filling of the left supraclavicular nodes was present in 40%, filling of the right nodes in 5%, and bilateral visualization in 2%. Axillary lymph nodes were seen in 2.5% and cervical nodes in 3%. Lymph nodes lying parallel to the thoracic duct were demonstrated by lymphography in 15.6%, retrosternal nodes in 4.2%, hilar nodes in 4.2%, and paratracheal nodes in 5.9%. If prophylactic treatment of lymph node groups other than the inguino-iliac and aortic is planned, it should be selectively applied to the nodes demonstrated on the lymphogram. These contrast-filled node groups are in direct connection with the aortic region and are therefore directly reached by malignant metastatic spread. In the case presented, the involved posterior mediastinal lymph nodes were demonstrated by lymphography done immediately after orchidectomy. Prophylactic irradiation of the inguino-iliac and aortic regions, but not of this particular node group, was performed. Tumor metastases in the posterior mediastinum and the right hilar region were demonstrated about three years later, whereas no signs of recurrency were present in the iliac and aortic node groups.

Surgical Removal of Metastatic Nodes

Surgical excision of metastatic lymph nodes in the aortic region followed by postoperative irradiation treatment may be performed in cases of embryonal carcinoma, teratoma, teratocarcinoma and choriocarcinoma.[3,14,19,20]

Chemotherapy

Chemotherapy is applied for palliative treatment in cases with generalized metastases. In *seminoma,* alkylating substances show good results. *Embryonal carcinoma, teratoma, teratocarcinoma* and *choriocarcinoma* are treated with a combination of alkylating substances (cyclophosphamide), antimetaboliser (methotrexate) and actinomycin D or with mitramycin alone.

Results

Out of the total of 74 patients, 57 were observed for more than two years. The presentation of this relatively small number of cases compared to the large series of 900 patients reported by Dixon and Moore is justified because lymphography was used to evaluate the extent of malignant metastatic spread. A two-year survival rate seems to be sufficient to judge the value of lymphography since most patients with a lethal course of this disease succumb within the first two years.[7]

Seminoma is a highly curable tumor. The two-year arrest rate in our series is 92% compared to Dixon and Moore's 93.6%. A slightly higher survival rate was observed in cases of *embryonal carcinoma* and *teratocarcinoma* of 54.5% rsp. 72.5% compared to 41.3% rsp. 52.1%.[6]

Conclusion

Although our case material (57 cases) is about 16 times smaller than that of *Dixon and Moore* (900 cases) the increase in the two-year arrest rate might be due to better tumor staging by lymphography. A five-year period of observation and more abundant case material are necessary to judge the actual influence of lymphography on the prognosis of malignant tumors of the testis.

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Whenever a man's friends begin to compliment him about looking young, he may be sure that they think he is growing old.—Washington Irving

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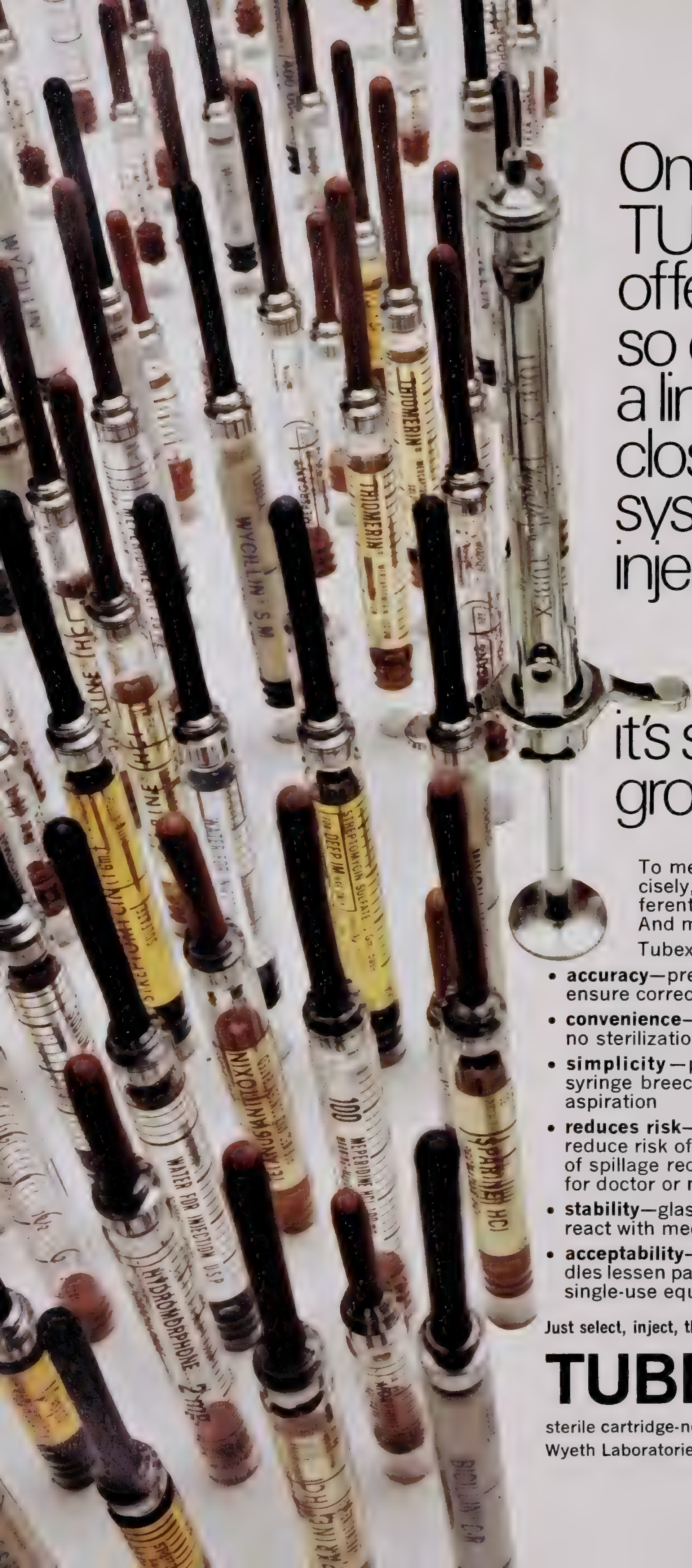
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Fracture Conference

A Subtrochanteric Fracture

THE CHIEF ADVANTAGE of a stable osteosynthesis is the possibility of early, pain-free, active mobilization, allowing for early full reconstitution of function of the damaged soft tissues. The results are particularly impressive in fractures of the forearm and the femur, as well as in intra-articular fractures.

The bone healing following an osteosynthesis depends upon the stability of the fixation and the viability of the bone fragments. Frequently these two basic prerequisites are not fully appreciated and failures result.

Every open reduction and internal fixation carries the danger of infection.

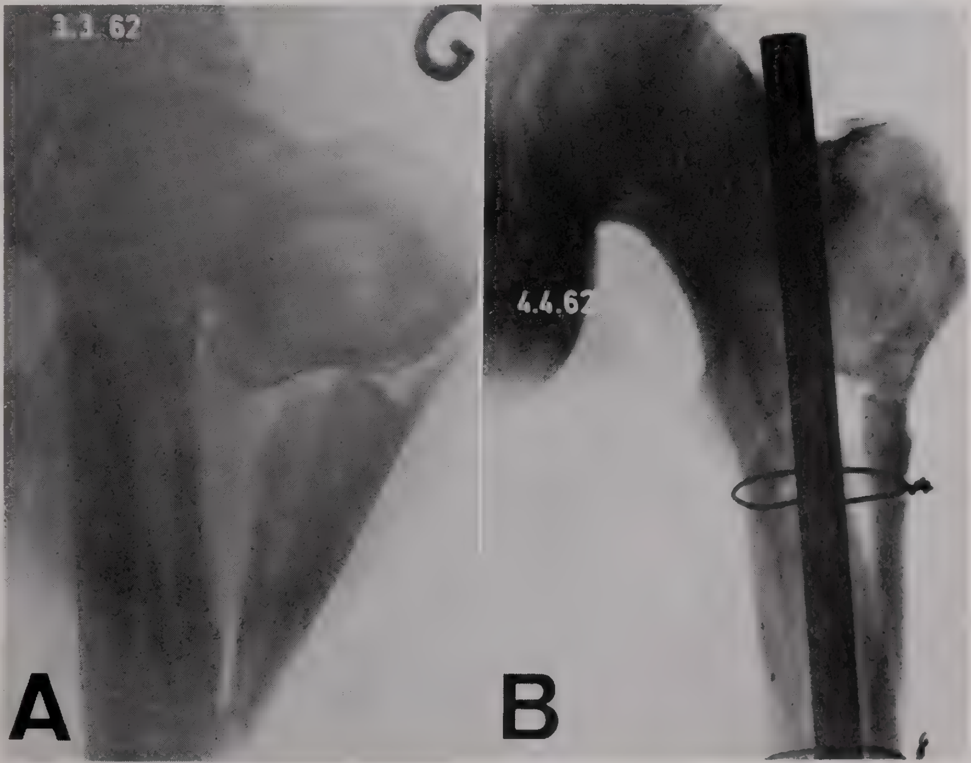

Fig. 1—(a-left) Intertrochanteric fracture; (b-right) Intramedullary nail and wire.

When one electively undertakes a procedure which involves a calculated risk, then one is obliged to obey all the basic principles in order to be as certain as possible of success. Only when an operation can assure a better result than non-operative treatment is the surgeon justified in undertaking an operative intervention.

The following case of a subtrochanteric fracture which had been operated upon seven times within five years, until union was finally obtained, illustrates well that a method should be employed only when one can be certain of success.

Case History

On March 3, 1962, a 24-year-old telephone fitter sustained a comminuted subtrochanteric fracture of the left femur (Figure A) in a ski accident. On March 4 this was treated with intramedullary nailing and a wire-cerclage (Figure B). On October 23 the metal was removed. On December 3 the patient sustained a spontaneous refracture (Figure C). On December 17, 1962, a Rush-nail was employed to secure internal fixation (Figure D). The nail was removed on November 8, 1963, with sound union of the fracture but with a marked external rotation deformity of the leg. Because of this, on August 16, 1964, a corrective intertrochanteric osteotomy was performed. This went on to non-union (Figure E). On June 15, 1965, one screw was removed and a cancellous bone graft inserted.

On August 30, 1966, the patient came under the care of an orthopedic surgeon (Figure F). The patient complained of pain in the left hip joint and was unable to bear weight on the left leg which was 3 cm shorter with very atrophic thigh musculature. The rotation deformity had been corrected; but in its place the patient had a considerable varus deformity and a pseudarthrosis where the intertrochanteric osteotomy had been carried out. On October 22, 1966, the final procedure was undertaken. This consisted of decortication, removal of the plate, and stabilization of the pseudarthrosis with a condyle plate and compression. At the same time an axial correction was made which consisted of 25° of abduction and 10° of internal rotation.

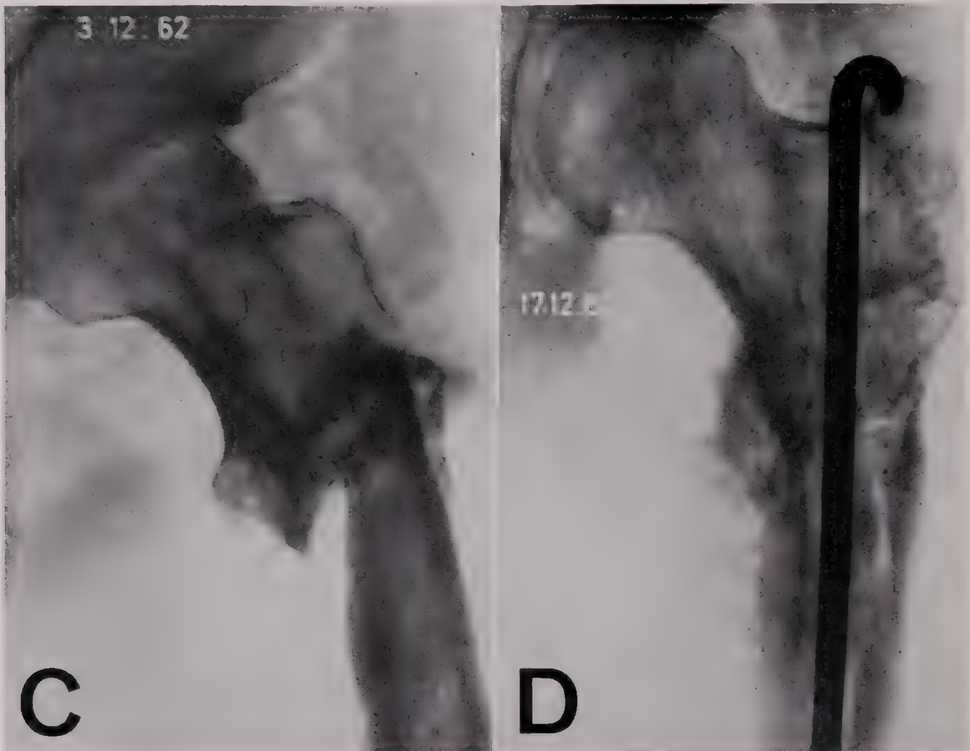

Fig. 1—(c-left) Refracture after removal of the nail; (d-right) Internal fixation by means of a Rush-nail.

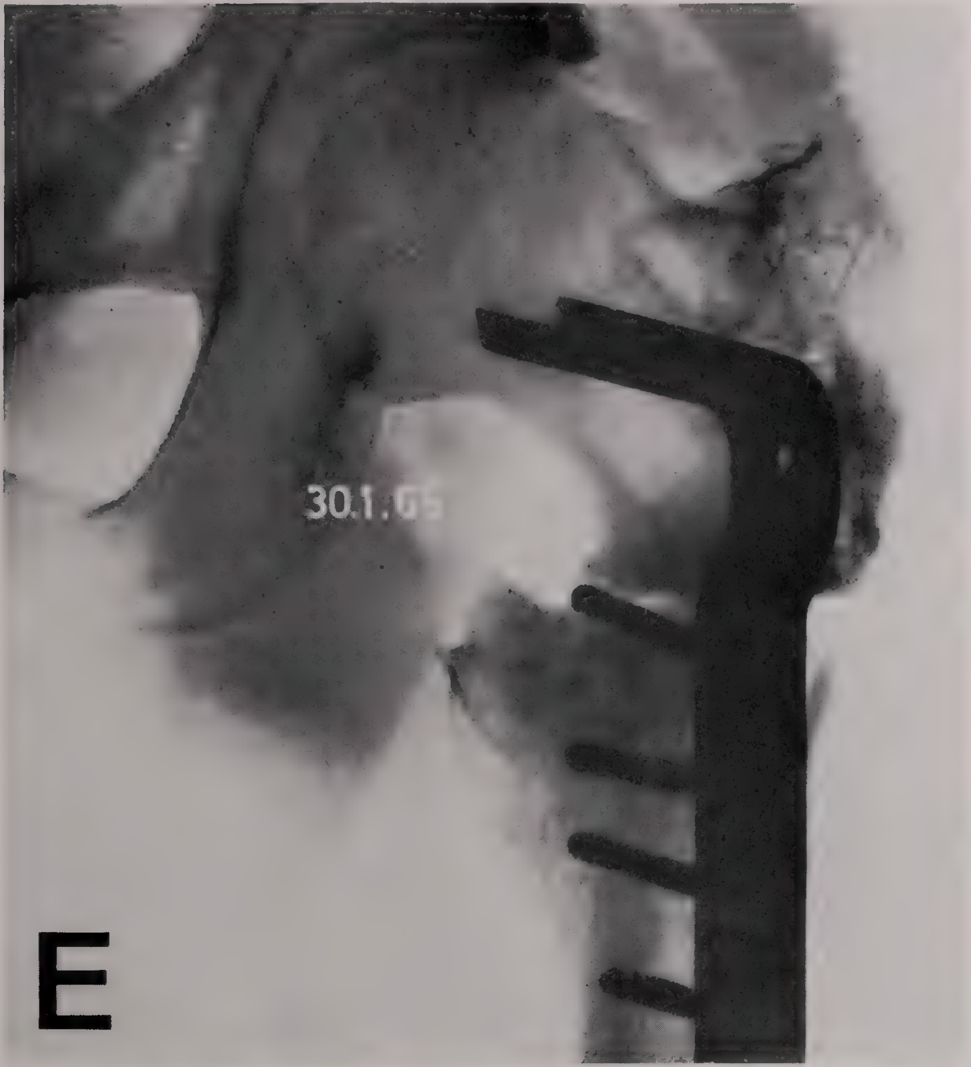

Fig. 1—(e) Intertrochanteric osteotomy with a screw in the osteotomy line.

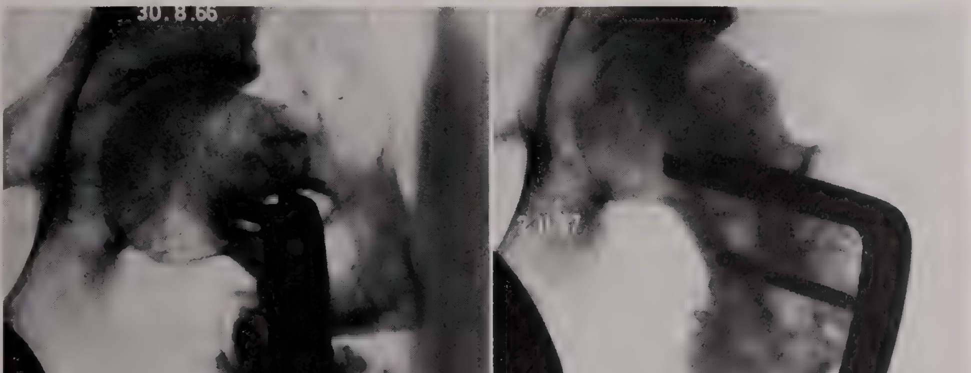

Fig. 1—(f-left) Non-union after intertrochanteric derotation osteotomy and removal of the screw in the osteotomy line; (g-right) end result one year after application of a right-angle compression plate.

At follow-up one year later, on November 2, 1967, the femur had consolidated and maintained the desired correction (Figure G). The patient was free of symptoms, had no disability, and was able to perform his previous work. The left leg was 1 cm shorter. The hip movements were: flexion/extension right 50/180, left 80/180; abduction/adduction right 120/60, left 115/65; external rotation/internal rotation right 30/30, left 40/10.

The treatment of this case took five and one-half years. It consisted of seven operations; and 76 x-rays had been taken. During this period the patient was totally incapacitated for 12 months.

Discussion

This case illustrates that, initially, all principles of a stable osteosynthesis were not observed. In sharp contrast stands the quick healing of the pseudarthrosis with correction of the deformity once a stable osteosynthesis had been carried out finally. One must say that the patient was particularly lucky that in the course of the seven operations he did not develop osteomyelitis.

Operative Indications

In a comminuted subtrochanteric fracture an open reduction and internal fixation are indicated only if it is possible to carry out such a stable osteosynthesis that after two weeks the patient can be ambulant and able to bear some weight on the extremity.

Intramedullary Nailing

An intramedullary nail cannot stabilize a subtrochanteric fracture, and the use of concomitant wire-cerclage frequently leads to partial bone necrosis.

Removal of the Metal

At the time of metal removal the bone was not fully consolidated and creeping substitution had not fully occurred. This led to the inevitable refracture. If incomplete consolidation is encountered at the time of metal removal, new internal fixation must be employed at that time in order to prevent refractures.

Rush-Nailing

A Rush-nail secures only an adaptation-osteosynthesis. When one employs a Rush-nail, reduction must be absolutely perfect and maintainable; otherwise deformities such as this will result.

Removal of the Metal

The fracture had consolidated, but a marked external rotational deformity was present. A corrective osteotomy should have been carried out immediately.

The Corrective Osteotomy

The surgeon had the indications for such an osteotomy, but unfortunately his technique left much to be desired. The blade of the plate, for the most part, was not in the femoral neck, which considerably diminished its holding power. The fragments were not accurately reduced and were not brought under compression. Furthermore, one screw had been inserted into the osteotomy fissure itself.

The Removal of the Screw and Cancellous Bone Graft

The loose screw which had been placed in the osteotomy fissure was removed and replaced with cancellous bone. In the presence of an unstable osteosynthesis and a pseudarthrosis, grafting alone could not be expected to lead to consolidation.

Decortication, Corrective Osteotomy, Compression Osteosynthesis

The procedure of decortication has been recently revived by Judet, but had already been described in 1936 by Naughton Dunn as the "shingling operation." It is particularly useful in secondary procedures and will substitute, as in this case, for cancellous bone grafting. The condyle plate was employed here as a tension band and the osteotomy was brought under compression. This time the blade of the condyle plate was placed axially in the centre of the femoral neck, and absolute rigid fixation with compression was obtained. The compression of over 100 kg led to a rapid healing of the pseudarthrosis, a phenomenon which we have already observed in hundreds of pseudarthroses treated only with stable osteosynthesis and compression without additional bone grafting, as long as we were dealing with a vascularized pseudarthrosis.

Summary

This case illustrates that the operative treatment of femoral fractures is a difficult intervention and that a stable osteosynthesis is difficult and can be achieved only when the basic principles, namely anatomic reduction and viability of the bone fragments are adhered to.

M. E. Müller, M.D.*
H. C. Meuli, M.D.*
Berne, Switzerland

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*Orthopedic University Clinic, Inselspital, Berne, Switzerland.

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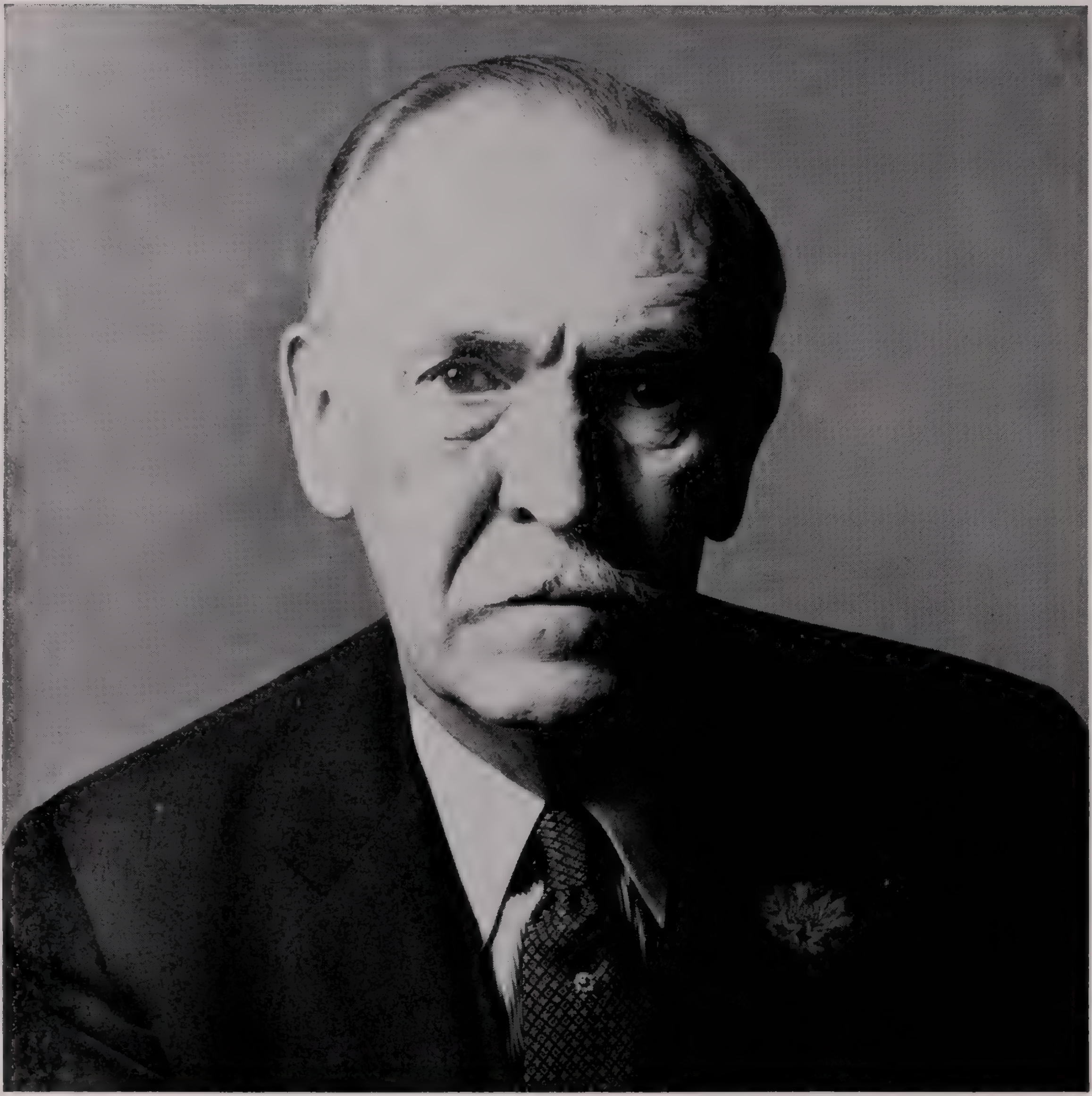
*Abe M. Goff, General Council, Post Office Department, 1957.

Gourmet But Not Gourmand

Great suppers do the stomach much offend,
Sup light if quiet you to sleep intend.
—Regimen Sanitatis Salerni

Editor's note: With economy and directness the School warns here that overeating breeds insomnia. This couplet should be memorized by gourmands—unless they intend to stay up all night.

Help the Needy!



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Cyanocobalamin	2.5 mcg.	1.5 mcg.
Intrinsic factor concentrate	8.0 mg.	—
Thiamine HCl	—	5.0 mg.
Thiamine mononitrate	10.0 mg.	—
Riboflavin	5.0 mg.	—
Niacinamide	50.0 mg.	—
Pyridoxine HCl	3.0 mg.	—
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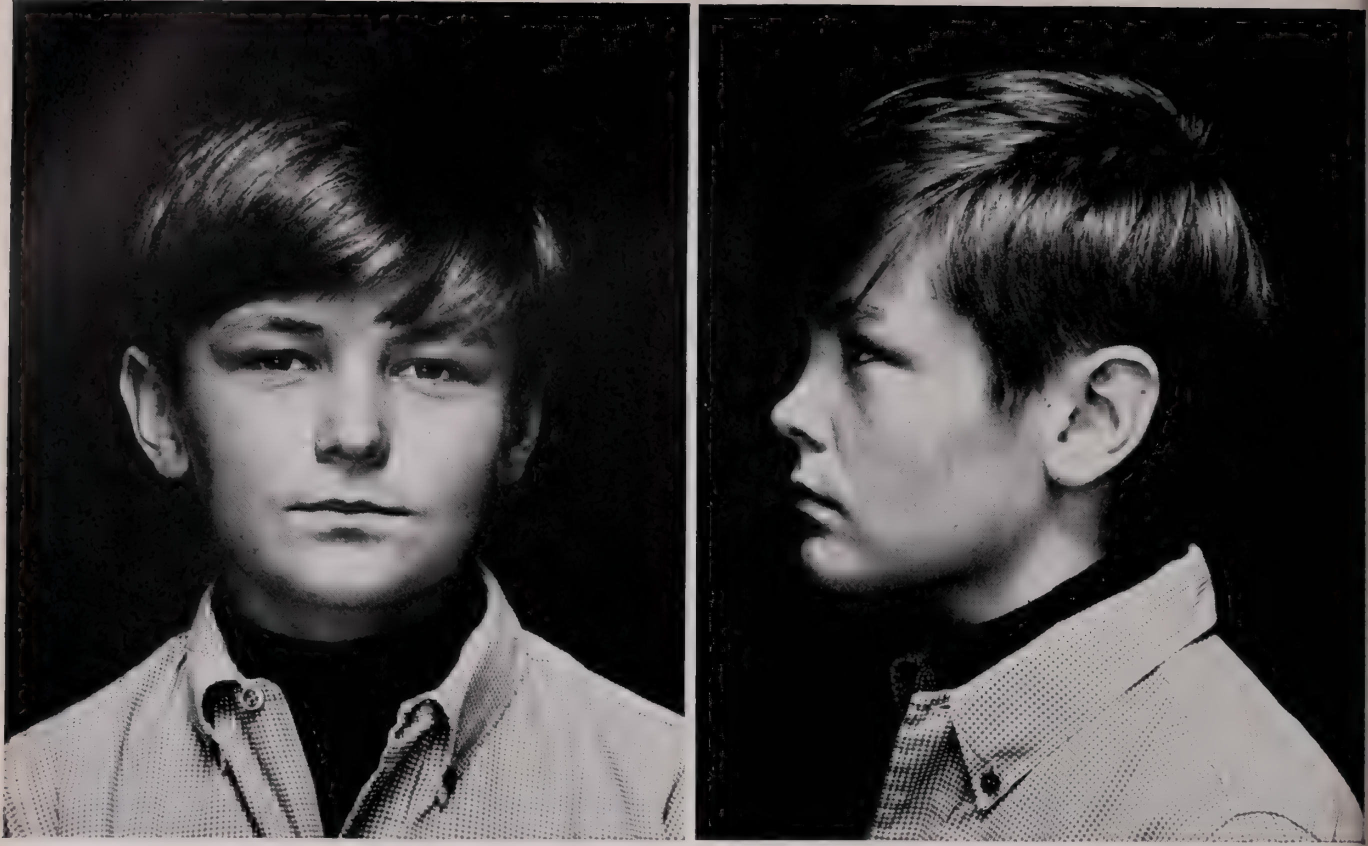

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Just forget your keys in your car one day.

Tempt some fourteen-year-old boy into going for a joyride.

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And taking your car might be the first time he's ever broken the law.

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Every time you do this you may keep a good boy from going bad.

Don't help a good boy go bad. Lock your car. Take your keys.

Grand Rounds

Infantile Cytomegalic Inclusion Disease
vs.
Chronic Gastrointestinal Disturbances

E. ROSSI, M.D.*
M. KÜHNI, M.D.*
Berne, Switzerland

UNTIL QUITE RECENTLY autopsy findings or the difficult demonstration of cells with cytomegalic inclusions in the urine sediment were the main means of establishing cytomegalic inclusion disease. Today diagnosis has become relatively easy and certain with the aid of complement fixation reactions with neutralization tests, and above all with the isolation of viruses from the urine. Since the clinical picture is very indistinct and permits only suspicion of the diagnosis, these tests are important. Here we shall consider mainly gastrointestinal disturbances. Chronic disturbances are fairly common in childhood, yet it is often impossible to make an etiological diagnosis.

In the past, virus diseases were held to be the cause of *acute* gastroenteritis, but the observation that the cytomegalovirus may also produce *chronic* gastrointestinal disturbances shows that virus diseases can likewise be responsible for such disturbances. Until now it has not been proved whether the presence of the virus is the cause of the symptoms or whether it is a mere coincidence. Similar problems have already been discussed in conjunction with toxoplasmosis and pneumocystis carinii. With this critical view in mind we present two cases of chronic gastrointestinal infections in which we found the triad: positive complement fixation reactions, cells with cytomegalic inclusions, and cytomegalic virus in the urine: cases in which we could exclude through further investigations other reasons for diarrheas.

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*Children's Hospital, University of Berne, Switzerland.

Background

In 1904 Jesionek and Kiolemenoglou[5] and shortly afterwards Ribbert[7] described for the first time the disease with the characteristic inclusions in the kidneys. It was first considered a protozoan disease, until in 1926 Cole and Kuttner[1] succeeded in transplanting the cytomegalovirus over seven generations of guinea pigs. Consequently these investigators believed in viral genesis. But it was only in 1956 that viral etiology was definitely established by Rowe[9], Smith[11] and Weller.[15]

Seifert and Oehme,[10] as of 1957, found 178 reports of children and 20 reports of adults with cytomegalovirus infection. Since then it has been possible, thanks to complement fixation reactions and by the isolation of viruses, to discover the incidence of infection in large groups of the population. It has been proved that cytomegalic inclusion disease is very common and that 50% of the population have had it before the age of 30[12,13] (Table 1), though infection may often remain inapparent.

TABLE 1

Incidence of Complement Fixation Reaction for Cytomegalic Inclusion Disease in the Course of Life (Stern, 1965, London)

up to 3 months	35%
1/2 to 5 years	4%
5-10 years	15%
10-12 years	47%
15-35 years	68%
36-60 years	81%

Many authors noted an affection of the gastrointestinal tract, especially in adults, most of whom had small or larger ulcerative lesions without specific localization.[6,14] Children often suffer from chronic, sometimes bloody diarrhea, without ulcers being detectable in vivo.[2,3,4] Symptoms are extremely variable. On the one hand small ulcers may not cause trouble; on the other they may produce severe, profuse bloody diarrhea necessitating bowel resection or internal therapy.

Incidence

The incidence of infection varies according to geographical and living conditions. Table 2 shows the incidence of positive complement fixation reaction for cytomegalovirus infection in children from one year to five years of age. These data are influenced not only by geographical circumstances, but also by population density, social conditions, and severe diseases aggravating the infant's general state of health. Also, pregnant women seem to be especially subject to cytomegalovirus infection. Table 3 summarizes these factors.

TABLE 2

Incidence of Positive Complement Fixation Reaction for Cytomegalovirus Infection in Children from 1 to 5 Years

District of Columbia (USA)	15%
Paris	41%
Helsinki	69%
Egypt	85%

TABLE 3

Factors Influencing Cytomegalovirus Infection

- Geographical aspects
- Density of population
- Social conditions
- Premature birth
- Severe illnesses
  - tumors: sarcoma
    - Hodgkin's disease
    - leukemia
    - thymoma etc.
  - immunosuppressive therapy in organ transplantation
  - accidents
- Pregnancy

Etiology of Cytomegalic Inclusion Disease

Virus etiology has been established by the above-mentioned authors. The viruses measure 113 millimicrons and are relatively insensitive to the effect of interferon. They also induce little interferon. Since the virus is present in the urine and saliva, it is likely that transmission is through these excretions, but it may also be transferred through a pathologically changed placenta. It produces nuclear inclusions which usually stain acidophilic with eosin dyes. The lesions have a homogeneous central area with a hazy peripheral zone and a thin clear halo.

Clinical Diagnosis

When cytomegalovirus infection is suspected, the tests in Table 4 should

TABLE 4

Methods of Examination with a View to Establish Cytomegalic Inclusion Disease

1. Complement fixation reaction
2. Neutralization test
3. Isolation of giant cells from the urine (not from the saliva or from the gastric juice)
4. Isolation of viruses from the urine
5. Isolation of cytomegalic cells from biopsy material
6. Isolation of cytomegaloviruses from biopsy material

TABLE 5

Clinical Aspects of Cytomegalovirus Infection

1. Congenital forms
   - a. oculo-cerebral localization
     - microcephaly
     - cerebral calcifications
     - cerebral infantile paralysis
     - microgyria
     - blindness
     - chorioretinitis
     - atrophy of the opticus
     - deafness
     - seizures
     - mental and corporal development defects
     - deformities
   - b. systemic localization
     - lung (interstitial pneumonia)
     - heart (myocarditis)
     - acute or chronic liver disease
     - gastrointestinal tract (ulcer)
     - spleen
     - hemopoietic organs (thrombocytopenia)
     - blood (hemolytic anemia)
     - skin (papulo-petechial exanthem)
     - bones (metaphysial distractions, sclerosis of the calcaneus)
     - endocrine glands (hypophysis, thyreoidea, pancreas)
2. Acquired forms
   - a. asymptomatic
   - b. influenza-like
   - c. ulcerative forms in the gastrointestinal tract
   - d. chronic liver disease
   - e. infectious mononucleosis
   - f. as a terminal complication in children with severe illnesses (leukemia, tumors)
   - g. hemolytic anemia
   - h. mental and corporal retardation
   - i. in organ transplantation (immunosuppressive therapy)

be made seriatim. Clinically two forms of infection are distinguished: congenital and acquired[8] (Table 5). It may, however, be difficult to differentiate between the two forms in practice. The two cases recorded below demonstrate the difficulty of diagnosis and the complexity of the disease.

Congenital Infection Case

Viruses may be transferred across the placenta to the fetus from a mother with viremia. The organs affected are mainly the brain, liver and blood-forming system. In some cases the mother already shows such symptoms as skin rashes, influenza-like illness, etc. In the child the main symptoms are erythroblastosis with thrombocytopenia and hepatosplenomegaly, suggestive of luetic disease, toxoplasmosis, listerosis* or septicemia. Only complement fixation reaction, virus isolation and cells with nuclear inclusions in the urine will permit a definite diagnosis. In some cases, cerebral symptoms will appear at once; in others they become manifest only at a later period. In final stages the disease is often associated with pneumocystis carinii.

In Case 1 the main symptom was bloody mucous diarrhea from the first days of life. A malabsorption syndrome was suspected. Dietetic treatment was not successful. Other findings such as corporal and mental retardation were interpreted as a result of the intestinal disturbances. Though the body was too small, it was well proportioned; therefore microcephaly was not noted. But on minute investigation retinitis pigmentosa was found, suggesting an infectious illness.

Acquired Infection Case

In the second case, that of M. P., intestinal symptoms did not appear until the second month of life. At the age of five months cutaneous symptoms completed the clinical picture. The patient developed a protein-losing enteropathy leading to severe hypoproteinemia and intermittently reappearing edema. Repeated infusions of albumin were necessary. This manifestation was quite extraordinary and has not yet been described. The cerebrum was not affected. The child was too small and showed mild hepatomegaly. Liver function tests were normal. Puncture biopsy revealed mild chronic hepatitis. Minute gastroenterologic investigations finally led to the exclusion of other causes of the chronic gastrointestinal disturbances. Since symptoms showed only after the second month of life and the cerebrum was not affected, we suspected acquired infection in this case. However, with symptoms appearing in the first weeks of life it cannot be decided with certainty just when the child was infected. Severe brain damage with deformities and the onset of severe symptoms immediately after birth suggest prenatal infection. According to the deformities the time of infection may be approximately determined.

A positive complement fixation reaction titer in the child is not in itself conclusive, given the great dissemination of the disease. Table 1 shows that a positive complement fixation reaction is quite common in the first months of life; generally the antibodies found have been passively transmitted by the mother. In children from six months to five years of age, a high titer usually signifies acute acquired infection. In older patients it may be a sign equally of previous and of new infection. Only the isolation of the virus and the cytomegalic cells from the urine or from biopsy material will establish the presence of disease. However, it has not yet been absolutely proved that the presence of the virus is really the cause of the sickness. It may be that it is of only secondary appearance.

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*See Test Your Word Score Page 89.

Combined with Pneumocystis Carinii

A very striking combination is that with pneumocystis carinii which we observed in two of our patients.

Children with chronic diseases or cerebral damage, whatever the symptoms, should be investigated for cytomegalic inclusion disease.

Chronic gastrointestinal disturbances are among the main problems in pediatrics. The symptoms of cytomegalic inclusion disease are extremely variable. On the one hand, infection may produce mild diarrhea which soon disappears; on the other it may cause severe gastroenteritis with blood in the stools and massive loss of albumin, as in our case. Even the ulcerative form of the disease may, in some cases, be discovered only incidentally at autopsy; in other cases it can lead to diseases resembling colitis ulcerosa and finally necessitate bowel resection. When gastroenteric symptoms appear, minute examination is indicated, including a series of barium enemas, biopsies, rectoscopy, loading tests with di- and monosaccharides and with gliadin, sweat tests, bacteriological examinations, duodenal intubation with a view to detect parasites and enzymes, etc. Only when other causes are excluded and complement fixation reactions and virus isolation from the urine are positive, may diagnosis of cytomegalic inclusion disease in the gastrointestinal tract be established.

Combination with other causes, especially with coli-infections, is quite common.

Unfortunately there is no satisfactory therapy available at present. Administration of corticosteroids and measles vaccine has been recommended in order to induce higher interferon blood levels. Our patient, M. P., was given rubella vaccine because of his low gamma globulin level and consequent danger of infection, but without success.

There is no definite prognosis: the fact that 50% of the population have been affected at some time before the age of 30 suggests that many infections remain inapparent or very mild. On thorough investigation of all children with chronic diseases, congenital cerebral defects, microcephaly, septicemia and hemolytic anemia in the neonatal period, the cytomegalovirus has often been demonstrated to be present.

Case Reports

Case 1, born June 28, 1966

Pregnancy and birth normal. Weight at birth 2,600 g. Very large placenta. The infant had difficulty in sucking, did not progress satisfactorily and appeared ill. At four weeks of age diarrhea started with bloody, mucous stools, and enlargement of the spleen and liver was noted. Various diets were tried: skim milk, soya milk, elimination of disaccharides and gliadin—with no success. The child showed developmental retardation; he had intermittent fever attacks due to bronchitis and otitis associated with febrile seizures.

Physical Examination: November 6, 1967

Severe dystrophy. Weight 7,000 g, length 71.5 cm, head 43.5 cm, all distinctly below the third percentile. On the skin, especially on the face, a strange reddish exanthem, slightly scurfy and spotty. The infant showed psychomotor retardation and corresponded developmentally to a child of nine months. Muscular system hypotonic. Skull slightly turricephalic. Otitis media on the right side. Ocular fundus with fine pigmentation from the back pole to the peripheral zone as a sign of retinitis pigmentosa. Bronchitis.

Laboratory Findings

Skin and liver puncture biopsies excluded reticulosis. Hemoglobin 10.5 gm. Hypochromia, white cell count and thrombocytes normal. Liver enzymes and bilirubin normal. Xylose and fat resorption, sweat test normal. Washermann reaction and examination for toxoplasmosis negative. Roentgenograph of the skull did not show any intracerebral calcifications. In the stools temporarily pathogenic coli 0 126 K 71 B 16. Lumbar puncture: 64/3 cells, 53/3 mononuclear and 11/3 polynuclear. Albumin 29 mg, glucose 50 mg percent. Cytomegalic antibodies in the serum 1:80. Cytomegaloviruses in the urine. Cytomegalic antibodies in the mother 1:40.

Clinical Course

Diarrhea persisted when coli-bacilli had disappeared from stools subsequent to treatment. Further dietary and antibiotic treatment was not successful. Diarrhea reappeared intermittently, often associated with new outburst of skin rashes.

Case 2, born April 27, 1966

Family history: an older brother was suffering from an itching eczema-like papular rash and often had infections until the age of two. Finally he had generalized edema, pleural effusion, ascites, and lost up to 0.5 g/die albumin in the urine. In the hospital he developed symptoms of bowel obstruction, finally necessitating laparotomy. Exitus after a few days. Diagnosis then was: nephrotic syndrome.

Personal history: pregnancy and birth normal. Intermittently reappearing diarrhea since the age of two months. Repeated bronchitis. At five months he developed a strange itching maculobullous exanthem. Edema on the extremities led to the diagnosis of hypoproteinemia.

Physical Examination: October 4, 1967

Cushingnoid appearance (after therapy with corticosteroids). Length 71.5 cm, weight 9,850 g, both far below the third percentile. On the lower abdomen and on both legs numerous red spots measuring up to 4 cm, slightly prominent and with signs of scratching. Liver 3 cm below the right costal margin. Abdomen notably protruding.

Laboratory Findings

Hemoglobin persistently too low, near 9.8 gm. Leucocytes between 6,700-18,900. Intermittent eosinophily up to 12 percent. No lymphopenia. Thrombocytes near 235,000. Xylose, saccharose, lactose, glucose and fat resorption normal. Duodenal intubation: no parasites, amylase and lipase normal. Sweat test normal. Biopsy of small intestine and rectum normal. Stool: no parasites, bacteriologic examination normal. Heavy loss of albumin into the intestine: after injection of 50 u Ci $\mathrm{Cl_3Cr^{51}}$, 10.5 % ($n = 1$) appeared in the stool seven days later. Notable elevation of the albumin turnover up to 462 mg/kg/die (normal = 0.145 %). Loss of albumin in the stool: 32.5 mg/kg/die (normal = 0). Liver enzymes (GOT, GPT, alcaline phosphatase), bilirubin and bromsulphthalein test normal. Liver puncture biopsy: mild chronic hepatitis. The most striking finding was a constant hypoproteinemia with albumin levels as low as 2.7 mg %. Electrophoresis: albumin 50 %.

Alpha 1:11%, alpha 2:22%, beta 12%, gamma globulin 5%. Pronounced diminution of immunoglobulin.

Ig A: 25 mg%	Ig M: 22 mg%	Ig G: 95 mg%
(n = 60 ± 8)	(n = 68 ± 17)	(n = 840 ± 120)

Examinations for Cytomegalic Inclusion Disease

CFR—titer in the mother 1:40. CFR—titer in the infant 1:30. Cytomegalovirus and cells with cytomegalic inclusions in the urine.

Clinical Course

Corticosteroids, antibiotics, elimination of food with animal albumin, gamma globulin, rubella vaccination did not influence the clinical picture. Severe hypoproteinemia with edema and ascites reappeared intermittently as well as diarrhea, sometimes bloody. In this course the general condition of the patient deteriorated and skin exanthem grew worse. One to two plasma infusions per week were necessary to keep the child alive.

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Mountebanks

Legitimate practice soon gathered in its train the quack, and serious medication, the fake nostrum. By 1711 a Mrs. Sibylla Masters of Philadelphia was making "Tuscarora Rice" out of Indian corn and selling it as a sure cure for consumption. . . . Seneca rattlesnake root appeared in 1739 and Dr. John Tennent was awarded 100 pounds by the Virginia Colony for curing pleurisy with it. It was a popular nostrum with itinerant vendors for many years. In 1745 there came to Philadelphia (which was early a thriving medical center) a Frenchman by the name of Francis Torres, with a Chinese Stone and sundry mystic powders that, he claimed, would cure with equal ease, snakebite, cancer, toothache, gout and labor pains! Then in quick succession followed a flood of fakes and quacks—Perkins metallic tractors, galvanic wires and Brandreth's pills, and a vast company of itinerant mesmeric healers who gave out medicine, cast horoscopes, and felt head bumps.

In cities the associations of doctors could fight these imposters, but in the country and on the frontiers they had an uncontested field. Once again we see the settled town representative combating the itinerant. Connecticut legislated against these imposters in her queer old law forbidding mountebanks. Other states subsequently followed suit, so that the itinerant medical faker has always been under the eye of the sheriff.*

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*Richardson Wright: Hawkers and Walkers in Early America, 1927.

Success in marriage is much more than finding the right person: it is a matter of being the right person.—B. R. Brickner

Most young car thieves start your car the same way you do.

(with your keys)

Half the cars stolen last year had the keys left in the ignition. And more than half the car thieves were kids under 18. You don't have to be an "old pro" to steal a car . . . when the keys are in it.

Young car thieves need your help to steal your car. Don't give it to them.

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TAKE YOUR KEYS.

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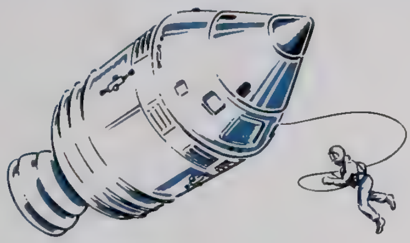

Man in space, now fait accompli, re-emphasizes the importance of Uro-Phosphate therapy. Research into the effect of space travel on the astronaut reveals that weightlessness causes loss of bone calcium. As the bones are required to bear less and less of the weight of the body they lose calcium, increasing the calcium content of the urine. When physical activity is reduced, the acidity of the urine should be adjusted to keep increased calcium in solution . . . . a prophylaxis to prevent kidney or bladder calculi.

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Each tablet contains: METHENAMINE, 300 mg.; SODIUM ACID PHOSPHATE, 500 mg.

Uro-Phosphate gives comfort and protection when inactivity causes discomfort in the urinary function. It keeps calcium in solution, preventing calculi; it maintains clear, acid, sterile urine; it encourages complete voiding and lessens frequency when residual urine is present.

Uro-Phosphate contains sodium acid phosphate, a natural urinary acidifier. This component is fortified with methenamine which is inert until it reaches the acid urinary bladder. In this environment it releases a mild antiseptic keeping the urine sterile.

Uro-Phosphate is safe for continuous use. There are no contra-indications other than acidosis. It can be given in sufficient amount to keep the urine clear, acid and sterile. A heavy sugar coating protects its potency.

Dosage:

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2 tablets on retiring will keep residual urine acid and sterile, contributing to comfort and rest.

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You provide prompt and continuous relief from symptoms of U.R.I. when you prescribe Novahistine Singlet. Novahistine Singlet is formulated to quickly relieve the fever and the aches and pains that so frequently accompany upper respiratory infections. And these continuous-release tablets provide a vasoconstrictor-antihistamine formulation to shrink swollen membranes and reduce congestion of the turbinates and sinuses.

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Novahistine® Singlet decongestant-analgesic

(Each tablet contains: phenylephrine hydrochloride, 40 mg.; chlorpheniramine maleate, 8 mg.; acetaminophen, 500 mg.)

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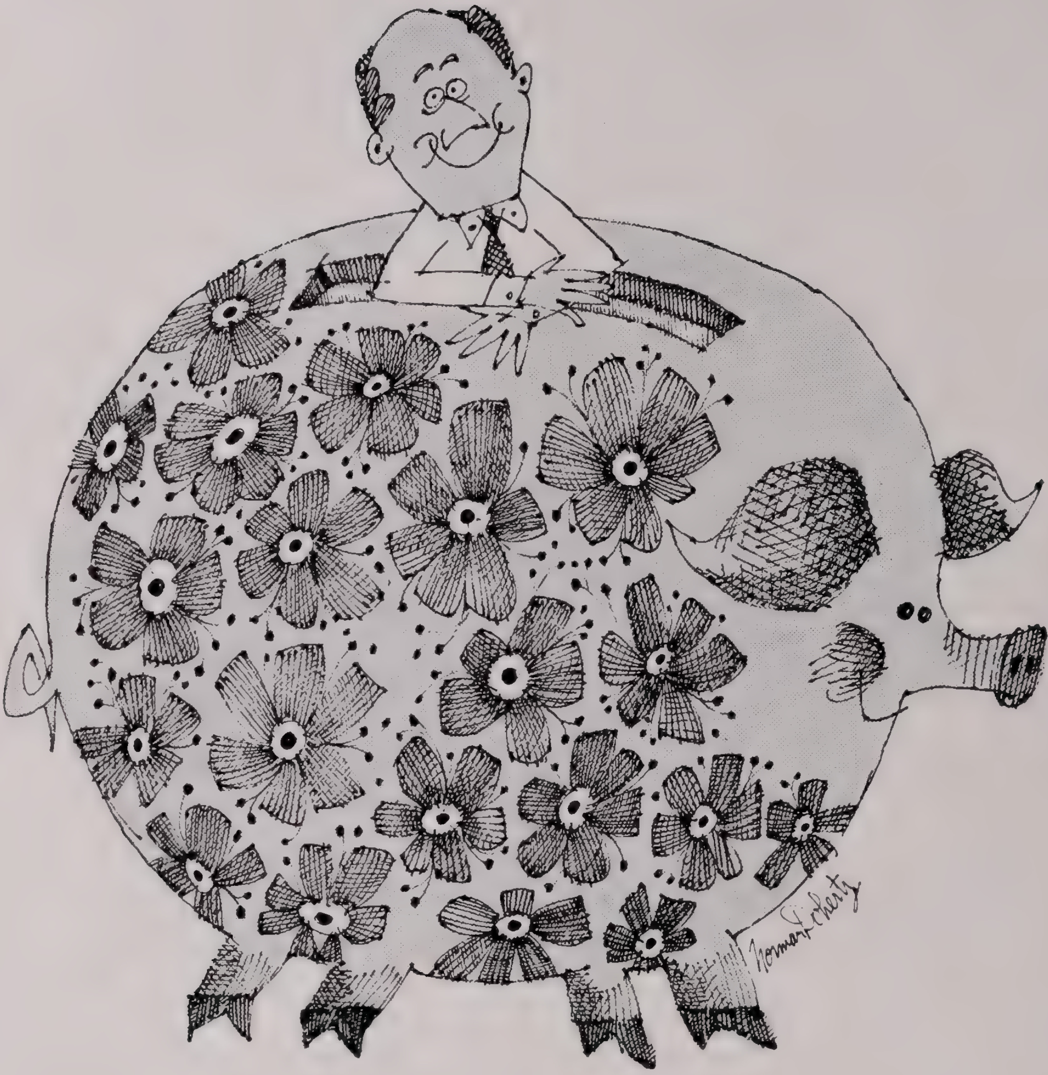

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Everyone dreams of a pleasant retirement. And practical people save for it. But what good are plans and dreams if you aren't around to enjoy them? Be smart and have a complete health checkup every year. 1,400,000 people living today are cured of cancer. And a yearly checkup could save many thousands more. Plan now to have a future. Make an appointment today for your health checkup.

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Allergic Reactions to Penicillins[*]

Advances in Understanding and Management

THE IMMUNOCHEMICAL mechanisms responsible for allergic reactions to penicillin in man have been the subject of numerous experimental investigations over the past ten years and have considerably advanced our knowledge on the mechanism of drug allergies. The interest in penicillin allergy stems from two main considerations. On one hand, allergic reactions to penicillins still represent a considerable nuisance in medical therapy. It may have been expected some years ago that other antibiotics would soon replace penicillins in therapy and thereby reduce penicillin hypersensitivity to a minor problem. But penicillins continue to represent about 30% of all administered antibiotics and their elimination from our therapeutic arsenal is less than ever predictable. With cumulative exposure of the population and with increasing use of penicillins and penicillin-like antibiotics for non-medical purposes, the absolute number of hypersensitive patients also appears to be rising. Allergic reactions to penicillin make up today about half of all allergic reactions to drugs in various countries of the world—as well in the United States as in Europe or in Russia. Penicillin is presently by far the most frequent cause of anaphylactic shock in man.[1]

A second reason for interest in penicillin allergy is because it provides a very suitable model to study the mechanism of immunological reactions and of drug allergies in man. In particular, the fact that the chemical structure of the responsible antigenic determinants may be known and various types of immunologically active reagents prepared enables us to study at the molecular level the mechanisms involved in the initiation or prevention of allergic reactions. It also becomes possible to follow the interplay of several types of immunoglobulins of the same specificity. However, continued research has indicated that even from one single relatively simple molecule such as penicillin, a large number of different antigenic† determinants originate. For that reason, the picture of the immunological response of man to penicillin has become increasingly complicated. Despite earlier hopes that the response of man to penicillins would be in fact a response to one or a restricted number of antigenic determinants it is now apparent that the immune response to penicillins involves a large variety of antigenic determinants and several types of immunoglobulins, yielding a complex picture and making interpretation difficult.

Allergic Reactions

In this paper we propose to review briefly the main clinical and immunological forms of allergic reactions to penicillin, the molecular mechanisms involved in the formation of penicillin antigens, as well as the consequences

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†See Test Your Word Score Page 89.

which recent advances should have on penicillin therapy and the attitude of the practitioner.

Forms of Immune Response

Various forms of immune response to penicillin in man have now been identified, only some of which will lead to clinical allergic manifestations. Contact with benzylpenicillin either in therapy or through hidden ways (e.g., milk, mycoses) induces in man various types of immunoglobulins with different biological and pathogenic properties and specific for quite a number of different antigenic determinants. It is not surprising therefore that several clinical forms of allergic manifestations to benzylpenicillin may be recognized. These clinical forms have different immunological features, and some of the confusion and discrepancies in this field are sometimes due to a natural desire for oversimplification.

A more precise analysis of the immunological features accompanying the various clinical forms of penicillin allergy has permitted us to understand why sensitization is much more frequent than allergic manifestations and why a prediction on the outcome of penicillin administration in a sensitized individual may be difficult. Immunological follow-up of allergic patients had also demonstrated the variability of individual responses and the importance of time in the evolution of the immune response. Accordingly, the immunological status of a patient cannot be established without taking into account various factors and applying simultaneously several types of immunological investigations.

Clinical and Immunological Forms of Allergic Reactions

Allergic penicillin reactions fall into several main groups, each of which has a different immunological pattern (Table 1).

TABLE I

Clinical and Immunological Features of Untoward Penicillin Reactions

Type	Interval	Symptoms	Specificity	Antibodies
No clinical reaction	Variable	None	BPO	IgM, ev. also IgE !
"Anaphylactoid" shock (iv. injection)	0-5′	neurological and sensoral	none	none
Anaphylactic shock	5-120′	collaps, B.P. ↓	Minor BPO	"Reagins" (IgE)
Immediate and accelerated urticaria	2-24 h.	urticaria	BPO	"Reagins" ↑ IgG → "clearing"
Serum-sickness-like disease	1-3 wks.	urticaria, fever arthralgias, etc.	BPO Minor	"Reagins" ↑ IgG → "clearing"
Chronic recurrent urticaria	variable	urticaria	Minor (?)	"Reagins"
Exanthema	5-10 days	morbilliform exanth.	BPO Others (?)	Delayed hypersensitivity IgM (?)
Hemolytic anemia	variable	anemia, Coombs +	BPO Others?	IgG, IgM (?)

"Immediate," "Accelerated" Reactions and Anaphylactic Reactions

"Immediate" reactions have a sudden onset, occurring within seconds or up to an hour after penicillin administration. They are usually followed by recovery but may end in death. The symptoms resemble those of anaphylactic shock in animals. There may sometimes be attenuated symptoms only, e.g., palpitation, vertigo, dizziness, perspiration, tingling of the tongue, ill-defined malaise, etc., which may subside or develop into severe vasomotor collapse. They may sometimes be followed by signs of cerebral damage.

The true anaphylactic shock with cardiovascular collapse should not be mistaken for the rather frequent "pseudo-shock" or "anaphylactoid shock" due to the accidental intravenous injection of procain penicillin or of large penicillin crystals. In such cases the onset is often noticed during the injection, with auditive and visual hallucinations and anxiety dominating the clinical picture. There is generally no real cardiovascular collapse.[3] So-called "accelerated" urticarial reactions occurring from one hour up to one to two days after penicillin administration are now usually classified together with sudden or immediate reactions. The character of the immediate reactions indicates that antibodies must be present in the patient as the result of previous exposure to penicillin. Such exposure may have been a decade or more previously.

"Late" Allergic Reactions

Strictly *cutaneous manifestations* of various types: generalized urticaria, erythemas and morbilliform exanthemas, erythrovesicular eruptions ("id-reactions"), and some rarer types, e.g., erythema nodosum, purpura, erythema multiforme, fixed drug eruptions, acute necrotic epidermolysis, periarteritis nodosa. Exfoliative dermatitis seldom occurs but may be fatal.

Serum-sickness-like reactions which usually combine urticaria and other skin lesions, fever, polyadenopathy, joint swelling and pain, sometimes angioedema. The latter often occurs separately but as an immediate reaction. The term of "late" reaction refers only to the delay between penicillin administration and the onset of the clinical manifestations; this does not indicate whether the manifestations are due to an immediate-type (antibodies) or a delayed-type (sensitized lymphocytes) mechanism. Erythematous and urticarial reactions are the most frequent, the latter accounting for more than half of the total penicillin reactions. In late reactions there may not have been any previous exposure to penicillin and the reaction occurs only after some days (usually five to 14) following commencement of a series of penicillin administration, during which time anti-penicillin antibodies and sensitized lymphocytes may have been formed.

Contact Dermatitis

Local application or exposure to penicillin may cause dermatitis. It is seldom accompanied by allergy to penicillin of the immediate type, although this is not excluded. It is usually observed among nurses and physicians handling penicillin preparations, and among workers in the pharmaceutical industry exposed to penicillin during manufacture. It also occurs frequently in patients exposed to prolonged local penicillin treatment, the risk of sensitization being particularly high when the drug is applied to macerated skin.

Other Rare Reactions

Acute psychotic syndromes ("anaphylactoid reactions"), pachymeningitis, gangrene and intestinal hemorrhage, temporary or permanent renal damage, liver necrosis, myocardial damage, acute pericarditis and isolated eosinophilias have been described. In certain individuals large doses of penicillin appear to induce hemolytic anemia by an immunological mechanism. The possibility that symptoms like nausea, vomiting, anorexia, convulsions, diarrhea, glucosuria, anuria, myocarditis, etc. may be toxic side effects of penicillin rather than caused by previous sensitization has been suggested.[1]

Antibodies and Immunological Tests

Humans in contact with penicillin may respond immunologically by the formation of antibodies, among which skin-sensitizing and hemagglutinating antibodies have so far been identified. Their properties, as characterized up to now, are shown in Table 2.

Skin-sensitizing Antibodies

7S gamma globulins have been reported to possess at least two different specificities: those that can be identified by skin test with the penicilloyl-polylysine antigen[4,5] and those identified by skin test only with benzylpenicillin. The existence of skin-sensitizing antibodies of various other specificities is demonstrated from skin test and passive transfer results with various penicillin fractions[6]; but the specific antigenic determinants reacting with

TABLE 2
Characteristics of "Anti-Penicillin" Antibodies

Characteristics	Immuno-globulin M (IgM)	Immuno-globulin G (IgG)	Skin-sensitizing antibodies, "reagins" "anaphylactic antibody" (SSA)
Sedimentation coefficient	19S	7S	75
Electrophactic mobility	$\gamma 1-\beta$	$\gamma 2$	$\gamma 1-\beta$
Thermostability	+	+++	—
Sensitivity to 2 mercaptoethanol	+++	—	+++
Agglutination of penicillin incubated erythrocytes			
in saline	+++	+	(+)
in serum diluent	+++	+++	?
Hemolysis of penicillin-incubated erythrocytes	—	—	—
Passive transfer in humans (Prausnitz-Kustner)	—	—	+++
Passive cutaneous anaphylaxis in guinea-pigs	—	++	—
Specificity	Penicilloyl Other Minor determinants?	Penicilloyl Other Minor determinants?	Penicilloyl Penicillin Other determinants
Pathologic role	Some exanthemas?	Blocking antibodies Hemolytic	Anaphylaxis Urticaria

these antibodies are not yet definitely identified. Skin-sensitizing antibodies specific for the major penicilloyl antigenic determinant are mostly associated with immediate and early urticarial reactions ("accelerated reactions") which arise within the first 48 hours after renewed penicillin administration (Table 1). Penicilloyl-polylysine skin-testing frequently reveals the presence of these antibodies (Table 3) and appears more reliable and safe than passive transfer (Prausnitz-Küstner).

Skin-sensitizing antibodies specific for the minor penicillin G antigenic determinants have been held responsible[7] for the majority of "sudden" anaphylactic reactions and can be detected through skin testing with benzylpenicillin. A positive skin test with benzylpenicillin seems more indicative of a potential anaphylactic reaction than a positive skin test with penicilloyl-polylysine. However, there is little doubt that one may also observe anaphylactic reactions due mainly or entirely to penicilloyl-specific skin-sensitizing antibodies, so that both major (penicilloyl) and minor determinants may be involved in anaphylactic reactions to penicillin. Skin testing with crystalline benzylpenicillin is of supplementary value to skin testing with penicilloyl-polylysine. Together they serve to detect both minor and major determinants.

The above considerations relate to early ("accelerated") urticarial reactions and "immediate" anaphylactic manifestations. The so-called "late" allergic penicillin reactions, including serum-sickness-like reactions, begin days

TABLE 3

Results of Skin Tests in Patients with Recent (< Two Months) History of Allergic Reaction to Penicillin

	Positive skin tests to:			
Reaction	PPL only	PPL and "minor"*	"Minor"* only	+ skin test
LEVINE & al.				
J Clin. Invest., 1966				
12 "Immediate"	0	5 (42%)	7 (58%)	100%
10 "Accelerated"	6 (60%)	4 (40%)	0	100%
11 "Late"	10 (91%)	1 (9%)	0	100%
16 "Chronic"	0	3 (19%)	13 (81%)	100%
19 "Exanthema"	1 (5%)	1 (5%)	0	10%
Positive to PPL : 39/68 = 58% (–exanthemas) = 37/49 : 76%				
Positive to "minor" : 20/68 = 29% (–exanthemas) = 20/49 : 41%				
103 No reaction, recent PN therapy	8 (8%)	1 (1%)	0	9%
117 No PN therapy in 2 years	5 (4%)	0	0	4%
DE WECK & al. 1965-1967	PPL only	PPL and BPN**	BPN† only	+ skin test
12 An. shock	3 (25%)	2 (16%)	2 (16%)	58%
17 Immediate urticaria (and accelerated)	11 (65%)	4 (23%)	0	88%
23 Serum-like disease	13 (56%)	7 (30%)	1 (4%)	92%
11 Chronic urticaria	4 (36%)	4 (36%)	2 (18%)	91%
21 Exanthema	3 (14%)	1 (5%)	0	19%
Positive to PPL : 52/84 = 62% (–exanthemas) = 48/63 : 76%				
Positive to BPN : 23/84 = 27% (–exanthemas) = 22/63 : 35%				
92 No history of PN allergy	4 (4%)	2 (2%)	1 (1%)	7%

*"Minor": 6,000 U. BPN/ml + 3.5 mg/ml benzylpenicilloate intradermal

†BFN: 200,000 U./ml scratch benzylpenicillin.

or weeks after penicillin therapy and are eventually not all associated with skin-sensitizing antibodies. This is especially true for late morbilliform exanthemas (Table 3).

In serum-sickness-like cases, on the other hand, the association with skin-sensitizing antibodies of penicilloyl specificity, detected by penicilloyl-polylysine skin test is very frequent (Table 3). Sensitization may, of course, arise during the course of penicillin therapy in previously non-sensitized individuals. Initially negative skin tests do not therefore exclude the possibility that "late" penicillin reactions will occur. On the other hand the relatively high percentage (5-10%) of patients without history of allergic reactions to penicillin found positive in penicilloyl-polylysine skin testing does not detract from the value of the penicilloyl-polylysine skin test, as such patients appear to possess in fact a latent penicillin allergy (see below).

Hemagglutinating Antibodies

7S or 19S immunoglobulins occur frequently with skin-sensitizing antibodies in sudden ("immediate") anaphylactic, early urticarial reactions and serum-sickness-like reactions.[8,9] High titers of hemagglutinating antibodies are also observed when penicillins and 6-amino-penicillanic acid are injected into rabbits. These antibodies have usually been found to be specific for the penicilloyl determinant. Significantly higher titers of hemagglutinating antibodies are found in patients with a history of penicillin hypersensitivity than in those without, or who have never received penicillin previously. It appears that such antibodies are merely an indicator of the immunological response and not the cause of penicillin allergy.

There is often no direct correlation between the amount of hemagglutinating antibodies and the results of skin testing. Hemagglutinating antibodies may be also found in patients without clinical allergy to penicillin; they are usually specific for the penicilloyl determinant but also for other antigenic determinants. With an especially sensitive hemagglutination technique, it has been claimed that anti-penicilloyl antibodies are found in 97-100% of the population of New York. It must be noted, however, that the titers found in more than 60% of normal people investigated are rather low. As the hemagglutination is observed in such cases only with the help of a high colloidal diluent (dextran-serum mixture) which favours non-specific hemagglutination, the conclusion that nearly 100% of the people possess "natural" anti-penicilloyl antibodies would still require confirmation by some other technique.

In some individuals with penicilloyl-polylysine positive skin tests who do not develop immediate anaphylactic reactions upon injection of penicillin there are high titers of hemagglutinating antibodies.[9] It has therefore been suggested that the hemagglutinating antibodies may act as "blocking antibodies," competing for antigen with the skin-sensitizing anti-penicilloyl antibodies, preventing or slowing down reactions due to tissue-fixed skin-sensitizing antibodies (SSA). In this view, a low hemagglutinating titer associated with a positive skin test to penicilloyl-polylysine would favour an immediate anaphylactic reaction on subsequent penicillin administration, due to the lack of "blocking" antibodies. On the other hand, a high hemagglutination-titer and a positive penicilloyl-polylysine reaction would then render unlikely the occurrence of an immediate anaphylactic reaction on subsequent penicillin injection, but would be compatible with an accelerated urticarial reaction.

Clinical Experience

Clinical observations support the experimental results and empirical conclusions in regard to the immunological mechanisms outlined above. It has thus been shown that patients with a past history of penicillin allergy and negative skin tests to both major and minor determinants experienced no immediate anaphylactic or accelerated urticarial reactions on subsequent penicillin treatment, suggesting disappearance of antibodies. It cannot be excluded, however, that some of these patients had never been sensitive in the first place. Patients with positive penicilloyl-polylysine skin test treated with penicillin usually fail to develop immediate anaphylactic reactions, although the incidence of severe accelerated urticarial reactions is at least 10-12% versus less than 0.5% in patients with negative penicilloyl-polylysine skin tests.

In some series[5] the incidence of severe generalized reactions in penicilloyl-polylysine-positive patients under treatment with penicillin was so high (42%) that this type of experiment had to be discontinued. The fact that a majority of patients with penicilloyl-specific skin sensitizing antibodies do nevertheless tolerate penicillin injections may, aside from the presence of "blocking" antibodies mentioned above, also be explained by the quantitative balance (varying with time and from patient to patient) between the number of skin-sensitizing antibodies present, the amount of eliciting plurivalent conjugate formed in vivo from penicillin, and the amount of penicilloic acid or unreacted penicillin reacting with skin-sensitizing antibodies as a free inhibiting hapten ("inbuilt inhibition"). This aspect is further discussed in the following paragraph.

Positive skin-reactivity to penicilloyl-polylysine and/or benzylpenicillin may be evanescent and disappear with time. Thus, in patients who had allergic reactions two to two and a half months prior to testing, the penicilloyl-polylysine skin test was positive in 90%, while in patients with allergic reactions five to 10 years previously the positivity was 25-35%. A similar transient pattern is seen after skin tests with benzylpenicillin antigen. The evanescence of the skin reactivity to the two antigens need not be parallel and appears to vary markedly from patient to patient. It is probable that the evanescence of skin-reactivity is associated with decrease or disappearance of clinical sensitivity to pencillin.

Sensitized Lymphocytes

Morbilliform exanthemas seem to be, aside from contact dermatitis, the main clinical manifestation of delayed-type allergy to penicillin. Sensitized lymphocytes seem to be demonstrated by the lymphoblastic transformation test, but there appears to be no absolute correlation between this test and the occurrence of delayed skin reactions upon intradermal injection of penicillin.

Molecular Mechanisms in Penicillin Allergy

It has been widely accepted since the time of Landsteiner that sensitizing chemicals of low molecular weight may induce the formation of antibodies only when firmly, preferably covalently,* conjugated to some large carrier molecule such as a protein. This conception was established on the basis of experiments with highly reactive chemicals (e.g., dinitro-chlorobenzene). The conjugation theory has been applied by analogy to molecules which are less or not at all reactive with proteins but which are nevertheless found to be allergenic. In the early days of penicillin therapy some of the allergic reactions observed were also attributed to impurities in the relatively crude preparations. With the use of highly purified crystalline penicillins, however, it soon appeared that allergic reactions were also due to the penicillin molecule itself. According to chemical knowledge prevailing in the late fifties, penicillin did not appear to have significant reactivity with proteins and to be readily able to form stable conjugates in vitro. Our research on this problem therefore became oriented primarily on reactive penicillin derivatives or metabolites.

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*See Test Your Word Score Page 89.

Penicillenic Acid

Penicillenic acid (Figure), a highly reactive degradation product which readily occurs in penicillin solutions, was considered for a while the main cause of sensitization to penicillins. However, the finding that antibodies induced by penicillin are mostly of penicilloyl specificity may be explained also if penicilloyl conjugates are formed by direct reaction of the penicillin molecule, without penicillenic acid as an intermediate. The penicilloyl (BPO) determinant has clearly emerged during the last years as the most frequently involved in penicillin allergy and has therefore to be regarded as a "major" antigenic determinant. On the other hand, the effective role of penicillenic acid present as an impurity in penicillin solutions and/or developing in vivo after penicillin administration in the formation of antigenic penicilloyl conjugates has now become somewhat less credible.

Reactivity of the β-lactam Ring

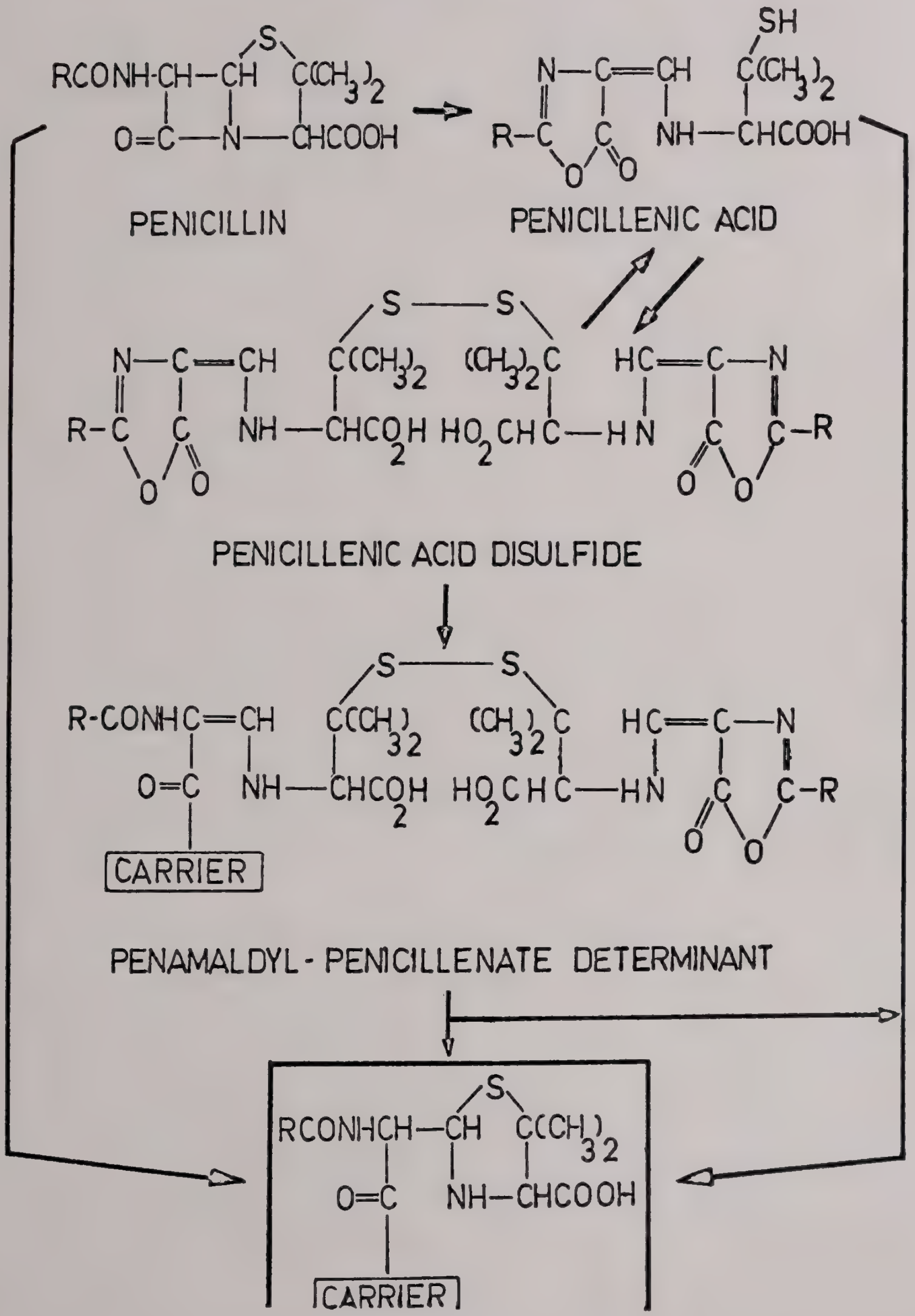
Various considerations have led us to believe that the direct reaction of the β-lactam ring of penicillin with amino groups is an important pathway by which penicilloyl-conjugates may be formed (Figure). Several chemical studies have indicated that penicillins may react "directly" with amino or hydroxyl groups under neutral pH and physiological conditions, forming thereby penicilloyl determinants.[2]

Whatever the respective importance of the "indirect" pathway via penicillenic acid or of the "direct" way via the β-lactam ring of penicillin to yield a penicilloyl structure, another possibility for the formation of penicilloyl groups is the reaction of penicillenic disulfide with amino groups (Figure).

With all these possibilities for its formation, it is not surprising that the penicilloyl group is a major determinant in penicillin allergy and that most of the antibodies encountered in patients undergoing an immune response to penicillin are of penicilloyl specificity.

There is evidence, however, that other antigenic determinants are also involved in penicillin allergy. On one hand, the penicilloyl group is relatively unstable and yields by successive degradation penamaldyl and penaldyl structures. On the other hand, a number of reactive derivatives such as penicillenic disulfide, penicilloic acid, penilloic acid, penilloaldehyde and penicillamine accumulate in penicillin solutions in vitro or are formed from penicillin in vivo. Skin reactions to benzylpenicillin and to derivates of penicillin

FORMATION OF THE PENICILLOYL DETERMINANT


PENICILLIN
PENICILLENIC ACID
PENICILLENIC ACID DISULFIDE
CARRIER
PENAMALDYL - PENICILLENATE DETERMINANT
CARRIER

Figure

such as penicilloic acid in some patients who are not hypersensitive to the penicilloyl determinant clearly indicate that other determinants participate in the sensitization process.

Impurities

The old assumption that allergic reactions to penicillin are in fact due to impurities has been recently revived,[10] as small amounts of penicilloylated proteins appear to be present in benzylpenicillin and 6-amino penicillanic acid (6-APA) preparations. Benzylpenicillin being extracted from a fermentation medium containing various types of proteins it would not be surprising that some impurities might be carried along in the extraction and crystallization processes. However, it has not been demonstrated that the exceedingly small amount of protein impurity present in some commercial benzylpenicillin preparations is sufficient to play a major role in sensitization of man to penicillins. The assumption that a penicillin solution devoid of any protein impurity will be less sensitizing is theoretically attractive; however, our experiments in animals demonstrate that the "purified" benzylpenicillin is as immunogenic as ordinary benzylpenicillin.

Furthermore, hydrolyzed crude benzylpenicillin, still containing eventual allergenic impurities, but where the β-lactam ring is open and no longer able to form penicilloyl conjugates, does not induce the formation of anti-penicilloyl antibodies.[6] It appears therefore that the bulk of the anti-penicilloyl response is induced by the benzylpenicillin molecule itself and that "purification" of this kind will neither abolish nor markedly reduce sensitization. Another argument speaks against the assumption that protein traces have played a major role in sensitizing man to penicillin. These protein impurities come from the fermentation medium and patients should be sensitized not only to penicilloyl but also to other determinants, e.g., mycelial proteins. However, this is mostly not the case.

The situation might be different in 6-amino penicillanic acid, prepared by enzymatic degradation of benzylpenicillin. By such a procedure, much higher amounts of penicilloyl-conjugates appear in the final products; hence the bulk of antigenicity of 6-amino penicillanic acid may effectively be due to these penicilloyl enzyme impurities.

Elicitation of Reactions

Let us now proceed to the elicitation of allergic reactions to penicillins, i.e., the elicitation of reactions in individuals who are already sensitized. In recent years, experiments with various types of conjugates and haptens of known chemical structure have clearly established that the number of antigenic determinants per molecule is a decisive characteristic, determining whether a conjugate will or will not elicit an immediate-type allergic reaction in a sensitized individual. It may be stated that truly monovalent antigens never elicit immediate-type allergic reactions, bivalent antigens may elicit anaphylactic reactions, whereas Arthus reactions require a least tri-or plurivalent antigens.

Therefore only part of the conjugates formed in vivo by an allergenic drug will function as effective elicitors; whereas all conjugates formed, including the monovalent ones, may function as sensitizers. In other words, the sensitization process requires only poorly substituted conjugates. In the elicitation phase, on the other hand, monovalent conjugates will act as inhibitors because they compete for antibody-combining sites with the bi- or plurivalent conjugates. The "inbuilt inhibition" of such a system is even reinforced when the original allergen (i.e., the unconjugated drug) also has some affinity for antibody. The free benzylpenicillin molecule has some affinity for anti-penicilloyl antibodies and is capable, when present in sufficient excess, of inhibiting reactions of penicilloyl specificity. It is therefore possible to calculate and to reproduce experimentally situations where the presence of small amounts of penicilloyl conjugates will be completely masked by the excess of free benzylpenicillin. This phenomenon of "inbuilt inhibition" is certainly responsible to a large extent for the observation that penicillin may often be tolerated even in patients who have a clear-cut immediate-type hypersensitivity to the penicilloyl-group, i.e., patients with a positive skin test to penicilloyl-polylysine. It also explains the relative capriciousness of allergic reactions to penicillin, the incidence of clinical reactions being much less than that of sensitized patients.

The elicitation of allergic reactions taking several hours to develop could probably be explained merely by conjugation in vivo. On the other hand, it is somewhat difficult to assume that enough plurivalent penicilloyl conjugates are readily formed in vivo to account for the dramatic onset of anaphylactic reactions.

We have therefore become interested in mechanisms by which "ready-made" eliciting antigens of penicilloyl or other specificities might eventually accumulate in penicillin solutions.[6] Considerable experimental evidence indicates that bivalent antigens, i.e., antigens carrying only two antigenic determinants per molecule, are sufficient to elicit anaphylactic reactions, although somewhat less efficiently than plurivalent antigen. It can therefore not be excluded that simple dimers of the penicillin molecule will eventually be sufficient to elicit anaphylactic reactions in highly sensitized individuals, the more as such dimers have actually been isolated from penicillin solutions. Furthermore, several chemical mechanisms may be visualized by which penicillin and penicillenic acid might react with themselves or with their degradation products to form various types of dimers and polymers. Finally, the presence of high molecular weight contaminants (e.g., protein, carboxymethyl-cellulose) in penicillin solutions might also lead eventually to the accumulation of eliciting antigens.

Purification procedures, based on chromatographic separation on Sephadex, leave in penicillin solutions numerous compounds susceptible of eliciting immediate reactions in sensitized patients. Whether the active eliciting fractions represent mostly small polymers or dimers capable of eliciting reactions as such, or highly reactive monomeric small degradation products eliciting only after conjugation in vivo, remains the subject of future investigation. The fact that highly sensitive patients are always hypersensitive to different antigenic determinants and to several chromatographic fractions of benzylpenicillin suggests that anaphylactically reactive patients are in fact those sensitized to the largest number of possible antigenic determinants and possibly also those sensitized to determinants non-cross-reactive with penicillin itself and therefore not protected by the "inbuilt inhibition" mechanism.

Attitude of the Physician Towards Penicillin Allergy

Although the advances in immunological understanding discussed above may explain some apparently unexpected observations encountered in clinical practice, they also oblige the practitioner to revise the very simplified equation: antigen = antibody = allergic reaction. From a practical point of view, the following attitude seems to be advisable at present.

Case History

No penicillin injection or administration should be performed without thorough inquiry about previous penicillin administration and eventual allergic reactions. When allergic reactions (especially urticaria) of unknown cause are mentioned by the patient, one should be aware of the possibility of hidden contacts with penicillin (milk, cheese, vaccines, mycotic infections).

Skin Tests

By scratch-test, prick-test or intradermal injection, one may elicit in hypersensitive patients within five to 20 minutes the formation of an itching wheel surrounded by erythema. Although advised in the past by some, a prophylactic skin test with penicillin solutions does not appear to be routinely used in clinical practice. An explanation for this rejection is the fact that such tests are found positive in only 20-30% of patients with a history of penicillin allergy. The poor results achieved with penicillin skin tests are often due to the fact that the penicillin applied or injected for the test has first to form a plurivalent conjugate in situ in order to elicit an immediate local allergic reaction.

It is not surprising therefore that complete plurivalent antigens such as conjugates prepared in vitro are much more effective test reagents. A peculiarly suitable conjugate is penicilloyl-polylysine, a small polypeptide molecule with penicilloyl determinants attached. This reagent can elicit specific local wheal-and-erythema reactions in a majority of sensitized individuals but is apparently unable to sensitize normal persons. Penicilloyl-polylysine is a much more effective reagent than penicillin itself to detect hypersensitivity to penicillin. Only about a third of the allergic patients with a positive penicilloyl-polylysine skin test also present a positive penicillin skin test. Furthermore, the penicilloyl-polylysine skin test appears to be safer than the skin test with penicillin itself.

Because of the eminently variable degree of hypersensitivity encountered in practice, it is not possible to recommend for skin testing with penicilloyl-polylysine one fixed dosage. With a high penicilloyl-polylysine dose there is a risk of causing systemic reactions in very highly sensitive patients. On the other hand, less sensitive patients may remain undetected with insufficient doses of penicilloyl-polylysine. Adequate investigation of skin hypersensitivity therefore requires cautious skin testing with progressively increasing test concentrations. This requires time and is hardly practical as a routine prophylactic procedure.

Although penicilloyl-polylysine is a more efficient skin test reagent than penicillin, penicillin should not be disregarded as far as skin tests are concerned. Occasionally patients are encountered who do react to penicillin but not to penicilloyl-polylysine. Such patients are apparently sensitized to other antigenic determinants than the penicilloyl group (Table 3). Yet such rare cases are important because they seem to have a frequent relationship with severe systemic reactions (anaphylactic shock). In our opinion, the performance of a scratch-test with aqueous benzylpenicillin (200,000 units/ml), together with a saline control, is certainly advisable prior to penicillin injection or administration. Such a procedure is even mandatory when a definite suspicion of penicillin allergy is present. On the other hand, the relatively risky intradermal injection of penicillin should be reserved for specialized allergists.

Serological Studies

As related above, patients immunized with penicillin produce several kinds of antibodies. The hemagglutinating antibodies do not appear to be responsible for skin hypersensitivity and allergic reactions but are nevertheless frequently present in patients having recently undergone an allergic reaction to penicillin. The hemagglutination reaction may therefore be used as objective confirmation of the diagnosis. The practical significance of the hemagglutination test may, however, be evaluated only together with the other information available, such as the date of the last penicillin administration and the results of the skin tests.

Numerous attempts to detect penicillin allergy by other immunological tests either with the serum or the leucocytes of allergic patients have been made within the last years.[1] Promising results have been obtained with several methods (e.g., basophil degranulation test, lymphoblastic transformation test, passive transfer to monkey). At present, however, no practical, reliable and simple in-vitro test to detect penicillin allergy is available.

Conclusions

For the present, practical advice may be summarized as follows:

A detailed case history concerning penicillin administration and allergic reactions should always be taken.

If there is the slightest suspicion of penicillin allergy in a patient, the indication of penicillin should be again carefully evaluated. In many cases, penicillin is not absolutely required or may be replaced advantageously by another antibiotic. If not, a scratch-test with penicilloyl-polylysine and/or penicillin may be performed.

Whenever possible in a case of suspected penicillin allergy, and especially shortly after an alleged allergic reaction, the case should be clarified by a specialist (extended skin tests, hemagglutination, serological investigations, etc.).

In principle, patients with demonstrated skin hypersensitivity to penicillin should never receive penicillin again. In some cases, however, the indication for penicillin therapy appears mandatory. It may then be justified to attempt a desensitization; but the results are usually transitory, and such procedures require special precautions justifying a short hospitalization. Physicians may be tempted to replace ordinary penicillin G by some of the new synthetic penicillins or by cephalosporins in the hope of reducing the incidence of allergic reactions. Cross-reactions between penicillin G and any of the other penicillins or cephalosporins on the market do occur, as shown by experience, but it is true that some quantitative differences in such cross-reactions exist. However, they are very difficult to assess statistically in a significant way.

For the present, a statement indicating that such or such a penicillin is less antigenic than the others does not appear scientifically justified. The specificity of the hypersensitivity for the side chain of penicillins may vary largely from one individual to another. Possible cross-reactions are unpredictable without a thorough immunological investigation. The safety rule for the practitioner is therefore to deny any penicillin therapy to patients having presented an allergic reaction to one or the other penicillins.

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Disease as Reprisal IV

Why were the Egyptians, innocent as well as guilty, smitten with boils?

The Lord was angry because Pharaoh would not let the Israelites leave Egypt.

And the Lord said unto Moses and unto Aaron, Take to you handfuls of ashes of the furnace, and let Moses sprinkle it toward the heaven in the sight of Pharaoh.

And it shall become small dust in all the land of Egypt, and shall be a boil breaking forth with blains* upon man, and upon beast, throughout all the land of Egypt.

And they took ashes of the furnace, and stood before Pharaoh; and Moses sprinkled it up toward heaven; and it became a boil breaking forth with blains upon man and beast. (Exodus 9:8-10)

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*Blains—blisters.

A sound mind in a sound body; if the former be the glory of the latter, the latter is indispensable to the former.—Tryon Edwards

It is sometimes as dangerous to be run into by a microbe as by a trolley car.—Dr. J. J. Walsh

A once-popular treatment for back pains was to have the seventh son of a seventh son stand or walk on the patient's back.

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Valium helps break this cycle of reflex spasm to local pathology—with these benefits: relief of discomfort as spasm is relaxed, increased range o mobility, faster return to more normal activities.

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When psychic tension or anxiety complicates th clinical picture of skeletal muscle spasm, the widely-recognized calming action of Valium ma also contribute to total patient management.

(Artist's conception of reflex arc.)

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dications: Tension and anxiety states; somatic mplaints which are concomitants of emotional ctors; psychoneurotic states manifested by nsion, anxiety, apprehension, fatigue, depressive mptoms or agitation; acute agitation, tremor, lirium tremens and hallucinosis due to acute cohol withdrawal; adjunctively in skeletal uscle spasm due to reflex spasm to local thology, spasticity caused by upper motor uron disorders, athetosis, stiff-man syndrome, nvulsive disorders (not for sole therapy).

ontraindicated: Known hypersensitivity to the ug. Children under 6 months of age. Acute rrow angle glaucoma.

arnings: Not of value in psychotic patients. aution against hazardous occupations requiring mplete mental alertness. When used adjunctively convulsive disorders, possibility of increase in equency and/or severity of grand mal seizures ay require increased dosage of standard anti- nvulsant medication; abrupt withdrawal may associated with temporary increase in frequency d/or severity of seizures. Advise against multaneous ingestion of alcohol and other CNS pressants. Withdrawal symptoms have curred following abrupt discontinuance. Keep diction-prone individuals under careful rveillance because of their predisposition to bituation and dependence. In pregnancy, ctation or women of childbearing age, weigh tential benefit against possible hazard.

ecautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation, have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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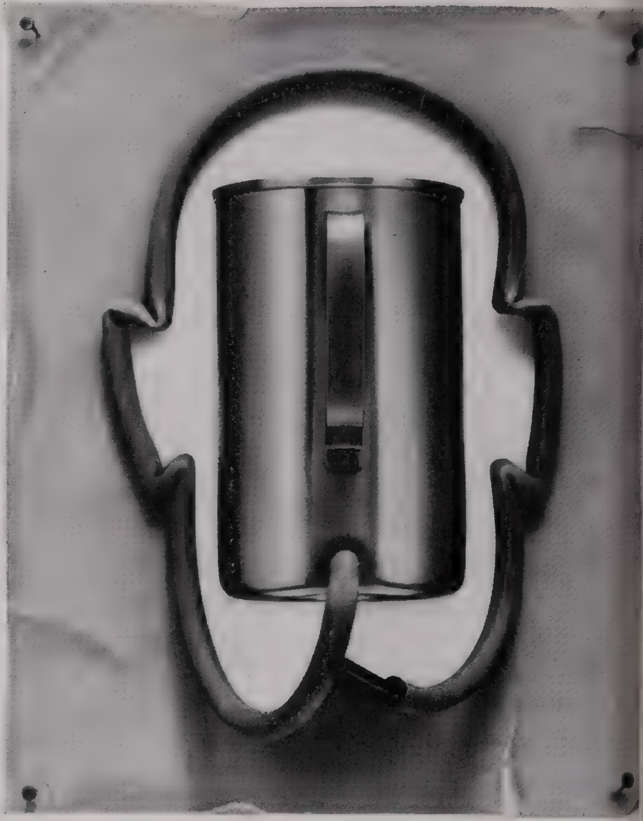

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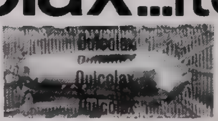

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D

Pediatrics

The Battered Child Syndrome

Part II. Social and Psychiatric Aspects

In Hennepin County from July 1, 1963, to July 1, 1968, 123 children from 116 different families were abused (See Table 1).

The disposition of these children was as follows:*

84 Remained at home or were returned home from the hospital.
26 Were placed under the custody of the Welfare Department.
12 Were placed by the courts in a foster home with legal custody given to the Welfare Department.
12 Were placed in foster homes per parents' request.
9 Were placed in relative's home per parents' request.
7 Died.

From January, 1968 to June, 1968, 37 children from 33 different families were reported to Hennepin County Welfare Department. The source of referral primarily came from physicians (53%). The remainder of the referrals come from a social worker and a variety of other sources (Table 2). These children were more frequently abused by the mother, and then in order: the father, stepparents, consort of parent, siblings and nonrelatives (Table 3). The social and ethnic distribution appeared to reflect the general population served by Hennepin County Welfare Department (Table 4). These families are primarily low-middle or middle income groups. Only six of 123 children were previously known to social agencies in the community.

The person who beats a child can come from any socioeconomic group or any walk of life. Of thirty representative cases in Hennepin County,[1] most have had some high school education. In two cases, the parents had some

TABLE 1

Number of Child Abuse Cases Reported to the Hennepin County Welfare Department—July 1, 1963 to June 30, 1968

DATES	NUMBER OF CHILDREN
7-1-63 to 12-31-63	6
1-1-64 to 12-31-65	15
1-1-65 to 12-31-65	9
1-1-66 to 12-31-66	22
1-1-67 to 12-31-67	34
1-1-68 to 6-30-68	33

TABLE 2

Source of referral 1-1-68 to 6-30-68 Hennepin County Welfare Department

Physician	10
Hennepin County General Hospital	10
Social Worker	9
Neighbor	3
Relative	2
Probation Officer	1
Principal	1
Nurse	1

TABLE 3

Abused By: (January to June, 1968)

Mother	16
Father	11
Step-father or step-mother	4
Non-relative	1
Mother's boyfriend, father's girlfriend	3
Sibling	1
Unknown	1

TABLE 4

Child's Race (January to June, 1968)

Caucasian	30
Negro	2
Indian	4
Other	1

Credit is given to Mr. Martin Coyne, Unit Supervisor, Child Protection Services at the Hennepin County Welfare Department, Child Protection Division, for his experiences listed herein.

*Some may have more than one disposition, such as living at home under the custody of the Welfare Department.

college education and in one case the assailant had a graduate degree. In four cases, the assailant was mentally retarded and four carried the diagnosis of being "mentally disturbed."

The average age of the female was twenty-six and the male, thirty. The majority of the cases reviewed within the experience of the Hennepin County Welfare Department revealed that these families are from any income group, any educational level, and are frequently estranged from the community.

The assailants often have no outward signs of neurosis or psychosis. They seem overprotective, cooperative, and neat. During the interview they reveal a lack of affect. They are usually immature, demanding, hypersensitive, egocentric persons who require immediate gratification of their desires. They exhibit a propensity for impulsive aggressive behavior when their needs are not met. Often beatings are precipitated by the child defecating in the tub or in his clothes, by crying, or by goading the assailant. Often these people were the subject of beatings, neglect, and rejection themselves[2,3] and are unwilling to accept responsibility. They are purported to be jealous of the child who is allowed to be dependent, while they themselves are not allowed by society to be dependent. Thus, they tend to take their frustrations out on the child by impulsively beating him.[4,5]

There is a high incidence of pre-marital unwanted pregnancy, marital instability, sexual promiscuity, minor criminal offenses (assault and rape), and occasional alcoholism.[3] These tendencies, however, cannot be considered causes of physical abuse to children.

These child beaters are sometimes classified as having character disorders, with little guilt or anxiety about the child who is hurt and with very little reaction when the event is reported to the police. The guilty party very often is the one who seems more "normal" during the interview.[6]

TABLE 5

Reporting a Child Abuse Case*

1. Call: a. Police department or sheriff
b. Welfare department, child protection division†
2. Follow above by written reports describing history, physical examination x-ray results, etc., to police and welfare departments

*As required by Minnesota State Law
†Social worker at your hospital can do this, if one is available.

Some are overtly psychotic, especially the female with post-partum psychosis or the male who "tries to take the family with him" during a suicide attempt. He usually lives, while the child dies.[7]

Reporting Procedures

When a physician discovers a battered child he is required by law to refer the case first by a telephone call and then by writing to the local welfare and police department (Table 5). When this is done, his legal responsibilities are absolved. The department then assumes the responsibility for the reported cases and investigates, follows through and makes disposition of the cases as it and the courts see fit. Where a social worker is present in a hospital, that person can help handle the details for the physician with the police and welfare departments. However, the physician must supply details of medical findings, such as history, physical, and x-ray findings.

In one series, most of the cases which came to the attention of the police did *not* come from physicians, yet one third of them were seen by physicians. Why do we not report more? It might be due to the following three causes:[8]

1. We do not recognize the syndrome;
2. We do not know what to do if we do recognize it, due to lack of knowledge of the law or methods of reporting, or worry about lack of proof (which is not our problem);
3. We do not care (probably rare).

(Continued Next Month)

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Reference may be secured from the authors.

Case Reports

Vascular Malformations of the Dura Mater

VASCULAR MALFORMATIONS such as saccular aneurysms and arteriovenous malformations are much rarer in the dura mater than in the brain. Several reports[1,3,4,6,7,10] concerning arteriovenous malformations, especially in the tentorium, have been made. These authors also describe the characteristic angiographic finding of the frequently dilated tentorial branches of the internal carotid artery. On the other hand, the true non-traumatic aneurysm of the meningeal arteries is very rare. *New* believes, as a result of his own observations and those of *Berk*, that Paget's disease of the skull, arterial hypertension and true aneurysm of the meningeal artery are a triad, whereby the aneurysm develops in the later years as a result of the hypertension and the reduced bony support of the meningeal artery. He corroborates his opinion with the observations of *Hassler* who found histologically in 45 autopsies 19 large and 45 smaller media defects. The better support of the meningeal artery by the firm tissue of the dura could, according to his interpretation, prevent the development of aneurysm in these arteries which incidentally have the same structure as the arteries of the brain.

The combination of saccular aneurysm with arteriovenous malformation in the brain is known but not frequently seen.[2,3]

Recently we have observed a patient with the combination of a non-traumatic saccular aneurysm of the middle meningeal artery and an arteriovenous malformation of the tentorium. As the case is histologically documented it appears worth presenting, especially since we have not found a similar one in the literature.

Case Report

It concerns a 41-year-old dysplastic* male (A.F.) with cryptorchism on both sides, multiple small fibroma of the skin and pharynx, and a body weight of 100 kilograms. Since early childhood he had suffered from headache, especially in the morning, which was increased by activity. Because of visual disturbances with diplopia and repeated vomiting he entered the clinic for further study.

Physical Examination

Striking findings included a large head (skull circumference 65 cm), papilledema of about 4 diopters on both sides, and a blood pressure of 150/105 mmHg. The right eye showed a weakness of convergence. Visual field: binasal quadrant defect and central scotoma. Visus: ri 1.0, le 1.25. The other neurological findings, as well as the hematological examinations and endocrine studies, were normal. No sign of Paget's disease of the skull.

Neuroradiological Examination:

Left carotid angiogram revealed a wide and long tentorial artery (A. Bernasconi and Cassinari) which led from the carotid siphon to an arteriovenous malformation in the tentorium. The venous drainage emptied into the sinus transversus (Figure 1). Injection of contrast media into the common carotid artery, by pulling back on the needle, showed, in addition, a large saccular aneurysm on the lateral

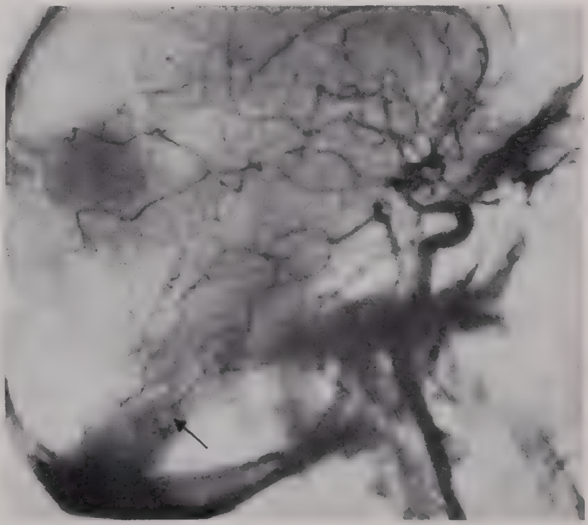

Fig. 1—Male, 41-years. Left carotid angiogram. Puncture of the internal carotid artery, lateral view of the arterial phase. Wide and long tentorial branch of the internal carotid with tortuous arterial channels at the periphery (arrow).

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*See Test Your Word Score Page 89.

wall of the middle cranial fossa, arising from the middle meningeal artery, which was projected directly over the carotid siphon (Figure 2).

The right carotid angiogram also showed a very wide and long tentorial artery but did not disclose a definite connection between this tentorial branch of the internal carotid and the arteriovenous malformation on the left tentorial border (Figure 3).

The pneumoencephalogram, by means of fractioned lumbar injection of air, demonstrated a free passage by a normally situated fourth ventricle, aqueduct and third ventricle. The left lateral ventricle was definitely widened but not displaced.

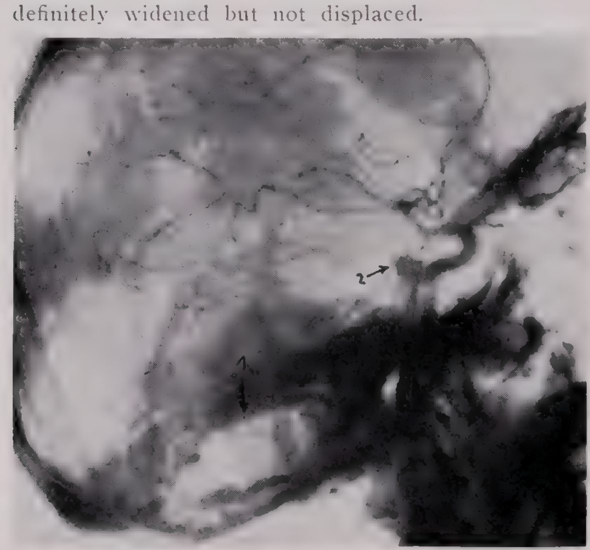

Fig. 2—Same case. Left carotid angiogram by injection of contrast material in the common carotid artery. The transverse sinus (1) is already visible because of arteriovenous shunting at the level of the malformation. As the external carotid artery is also filled, a large saccular aneurysm of the middle meningeal artery is seen in the dura of the middle cranial fossa (2).

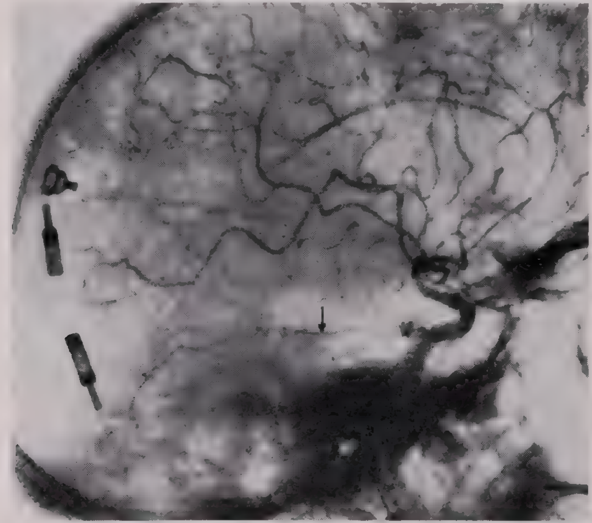

Fig. 3—Same case. Control angiography on the right side after atrioventricular shunt procedure. Large tentorial branch of the right carotid artery (arrow) without any visible connection to the arteriovenous malformation on the left side of the tentorium.

Operation:

Because of the increased intracranial pressure with marked papilledema and continuous vomiting an atrioventricular shunt (Spitz-Holter) was performed. Although the operation was simple and without complications the patient continued vomiting on the following days and became somnolent. Neuroradiological revisualization (Figure 3) did not disclose any change in the findings and there was no reason to suspect a hematoma, as the ventricular fluid was clear. A normally functioning shunt was observed. After fourteen days of assisted respiration the patient expired.

Autopsy of the Brain

The brain weighed 2,100 g and showed signs of tentorial herniation with internal hydrocephalus on the left side. The angiographically detected saccular aneurysm with a diameter of about 10 mm was found on the inner surface of the dura mater of the left middle cranial fossa (Figure 4).

Microscopic Findings:

The left middle meningeal artery was microscopically a normally developed typical arterial vessel without significant pathological changes in the wall. At the mouth of the aneurysm the intima of the arterial wall showed a diffuse fibrous thickening. The internal elastic lamella was mostly very well developed and wavy, but here and there widely split and interrupted. The outer wall showed a mild degree

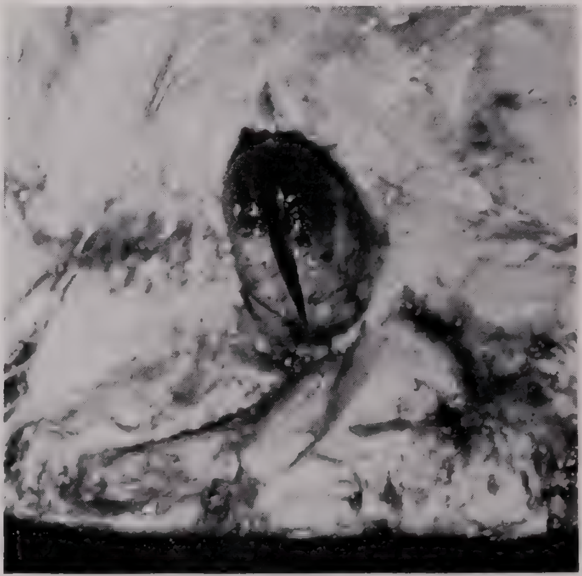

Fig. 4—Macroscopic appearance at autopsy (Nr. 366/67). Saccular aneurysm on the inside of the dura of the middle cranial fossa. The aneurysm has been opened.

of fibrosis and hyalinosis.

This vessel led into a dilated saccular aneurysm with a very thick, vasculated wall surrounded by dura. The intima was moderately cellular, showing diffuse fibrous thickening with slight hyperplasia of the smooth muscle. The internal elastic lamella was broken up and consisted of layers of varying thickness widely interrupted and distorted in some places. A medium was not distinguishable. The outer wall layers were moderately fibrous and partly hyaline.

The left tentorial branch of the internal carotid artery was a moderately thick-walled vessel of the arterial type with intact structure. The endothelium was missing in a few places.

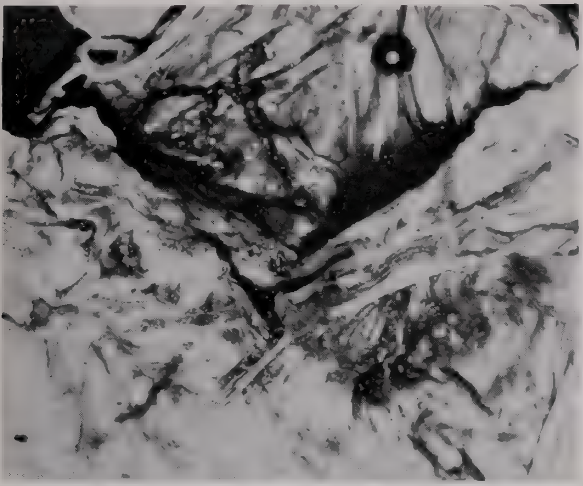

Fig. 5—Macroscopic appearance of the arteriovenous malformation in the left tentorium at autopsy. Superior longitudinal sinus with thickened wall (arrow).

The intima showed marked diffuse as well as plaque-like fibrous thickening. The internal elastic lamella was slightly reduplicated in several places. In microscopic sections from the region of the radiologically localized arteriovenous shunt between the A. Bernasconi and the left sinus transversus (Figure 5) one could recognize a saccular dilated vessel with a moderately, partly concentric, partly locally thickened, somewhat edematous wall. In the middle and outer layers the internal elastic membrane was interrupted, folded, broken up and in places hardly distinguishable. In the surrounding area were several smaller vessels of arterial, venous and transitional type, as well as slit-like cavities lined with endothelium without a true wall. The findings correspond to an arteriovenous malformation.

The microscopic picture of the macroscopically thickened confluens sinuum showed a dilated vessel with fibrous thickening and vascularization of the wall, with very little smooth muscle.

Comments

The question whether or not a direct causal connection exists between the arteriovenous malformation of the dura, size of the skull, increased intracranial pressure and remarkably increased brain weight is of special interest.

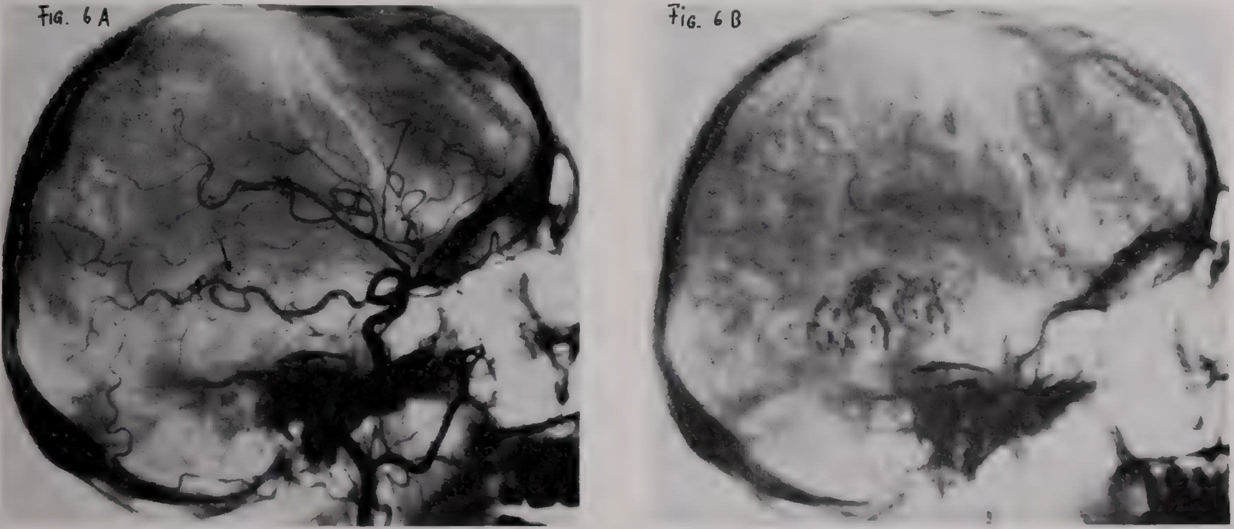

Fig. 6—Female, 28 years. Left carotid angiogram by puncture of the common carotid artery. (A—left) Lateral view of the arterial phase. Pathological vessels arising from the posterior cerebral artery (arrow). (B—right) Contrast retention in the wide sinusoids of the tumor. The contrast-filled cavities remain unchanged over a long period. Cavernous angioma of the tentorium.

A hydrocephalus with arteriovenous malformation of the dura has been described by *Newton* et al. and *Van der Werf*. Considering the wall changes of the confluens sinuum pointing to an increased load, it does not appear impossible that a long-lasting increase in pressure on the venous side could act as a chronic block resulting finally in a hydrocephalic enlargement of the left lateral ventricle.

A further, very rare vascular malformation of the dura is the cavernous angioma, which is well known in the cerebrum (*Russell* and *Rubinstein, Zülch*). The angioma has no extra development of supply vessels and the vessels of these cavernous angiomas of the cortex usually show up very weakly or not at all in the angiogram (*Krayenbühl* and *Yasargil, Tönnis* and *Schiefer*).

The following case report concerns an angiographically detected and histologically verified cavernous angioma of the dura:

Case Report

A 28-year-old housewife was taken ill with headache after the birth of her first child. Examinattion did not reveal any important neurological defect. Because of suspicion of post-partum sinus thrombosis she was sent for angiographic study

Angiographic Finding

The left carotid angiogram revealed a tumor (5x3x3 cm) above the tentorium and the left petrous bone (Figure 6 a-b). The pathological vessels arose from the posterior cerebral artery; the tentorial branch of the internal carotid artery was very thin and played only a small part in tumor vascularization. Already during the arterial phase large cavities containing contrast material were seen in the tumor and remained visible more or less unchanged until the last venous phase, without the appearance of a tumor stain as in cases of meningiomas. Veins could not be distinguished in the angiogram.

Operation Finding

The patient was operated and the tumor removed (Dr. Reichenbach). It sat with a broad surface on the tentorium, sharply separated from the brain and surrounded by a capsule. During removal massive arterial bleeding occurred, especially from the attachment of the tumor to the tentorium. The patient recovered completely from the operation.

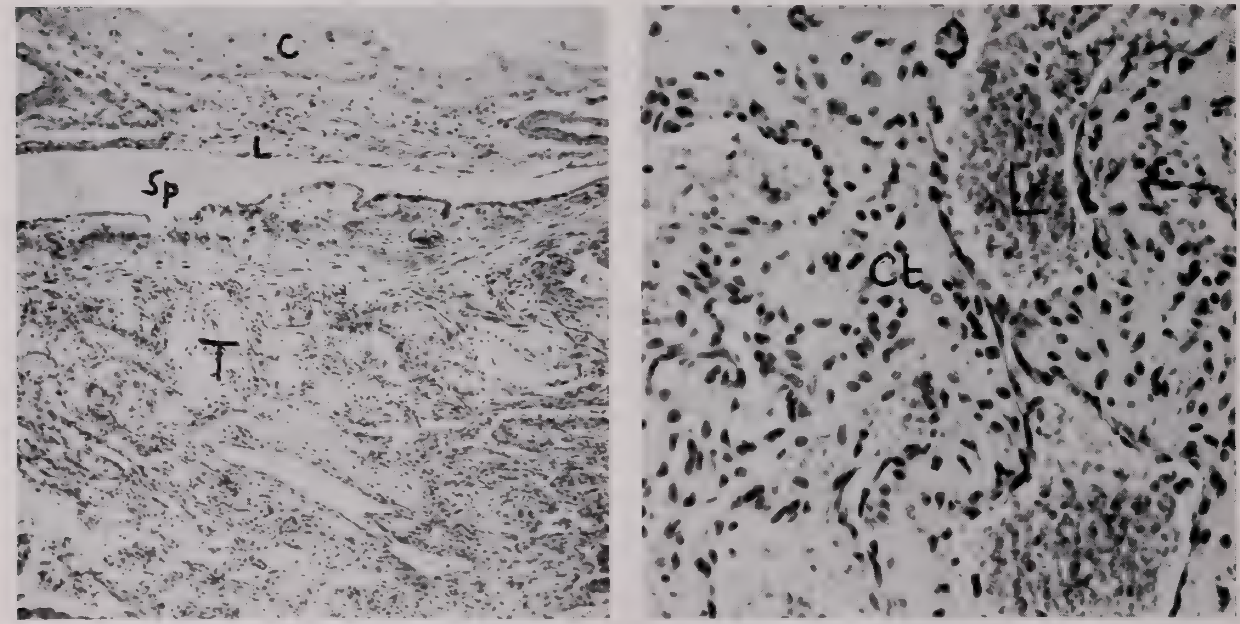

Fig. 7—Same case. Microscopic appearance of the tumor (cavernous angioma of the tentorium). Prot. Nr. 22487/67, Department of Pathology, foto Dr. Kraus-Ruppert.

A—left C = cortex cerebri.
L = leptomeninges.
Sp = subdural space.
T = cavernous angioma. (H and E, x 25)

B—right Between connective tissue (Ct) blood-filled lacunes with endothel (L). (H and E, x 100). Structures characteristic of a meningioma could not be found in the tumor.

Pathologic Findings

Histologically the tumor consisted of moderately and poorly cellular connective tissue containing many dilated sinusoidal vascular spaces, lined by a layer of flat dark cells. The outer surface of the leptomeninges was turned toward the tumor (Figure 7). Histologically it was a cavernous angioma without any indication of a meningioma.

McCormick and *Boulter* have collected three cases from the literature and have reported two additional cases detected by chance at autopsy. No angiographic examinations had been made.

Summary

Both the presented cases illustrate that essentially the same vascular malformations can occur in the dura as well as in the brain; they are, however, considerably rarer in the dura mater.

A case of combination of saccular aneurysm and arteriovenous malformation of the dura mater and a case of cavernous angioma of the tentorium are reported. Both patients were examined angiographically and histological studies were made.

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To The Young Practitioner

Need I remind you of the importance of punctuality in your engagements, and of the worry and distress to patients and their friends which the want of it occasions? One of my old teachers always carried two watches, to make quite sure of being exact, and not only kept his appointments with the regularity of a chronometer, but took great pains to be at his patient's house at the time when he had reason to believe he was expected, even if no express appointment was made. It is a good rule; if you call too early, my lady's hair may not be so smooth as could be wished, and if you keep her waiting too long, her hair may be smooth, but her temper otherwise.*

---

*Oliver Wendell Holmes.

He whose blood is red, whose muscles are hard, whose sleep is sound, whose digestion is good, whose posture is erect, whose nerves are steady has a good bank account in life.—Calvin Kendall

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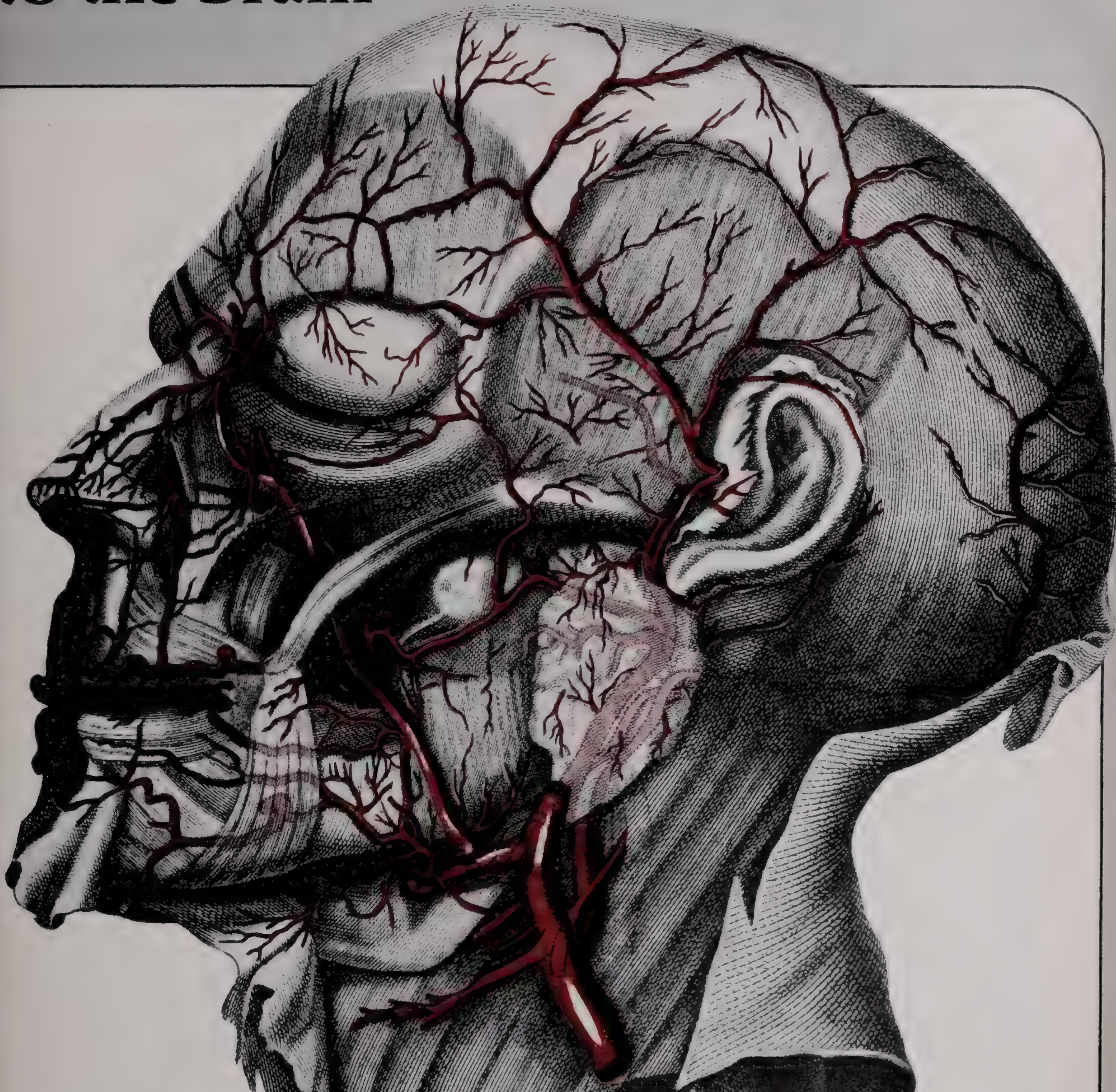

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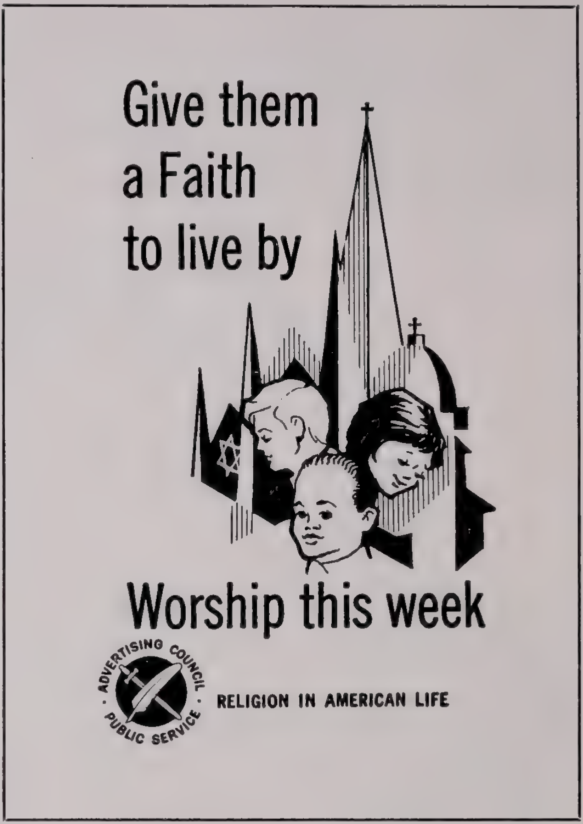
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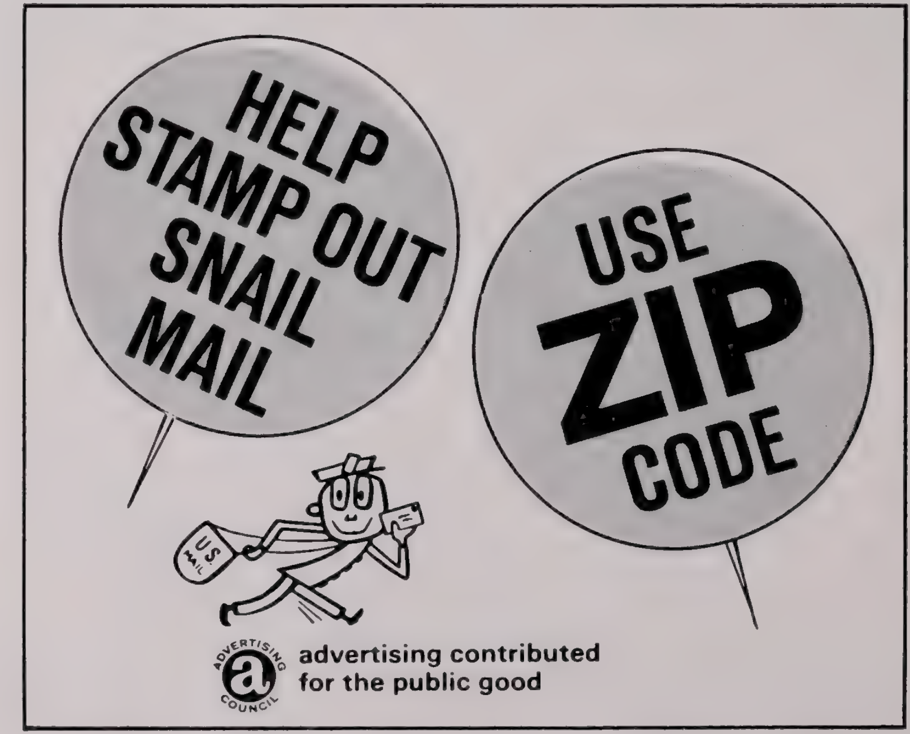
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Special Article

Berne—Queen of Swiss Cities

GUIDO SCHMEZER, Ph.D.*
Berne, Switzerland

EVER HEARD OF SWITZERLAND? — no not Sweden. Sweden is a different European country, although often confused with Switzerland by Americans. Sweden is farther north and has only one national language. We have four.

So you know Switzerland? William Tell, cheese, chocolate, watches, yodels—but please don't say leather pants! Leather pants are definitely Bavarian or Tyrolian; in Switzerland they are worn only by foreign tourists.

I am not going to tell you about Switzerland —I just wanted to make sure that you get your bearings: small Alpine democracy jammed between France, Germany, Austria and Italy.

The capital of Switzerland is Berne—so we Bernese are capitalists. But Berne is also a community—so we are also communists. The result: we are neutral.

Have you got a map within easy reach? If it is a world map, you will probably find only a very tiny patch of color representing Switzerland, and in the middle of this patch a microscopic dot indicating Berne. If the map is larger, Zurich and Geneva might also be designated, maybe even Basel and Lugano. Berne is only the fourth largest of these cities, yet the most important of all of them. This is confidential. Don't tell the others. They are jealous.

To make you understand and fully appreciate the importance of our city, I feel obliged to give you some historical facts.

History

At school you learn that Berne was founded in 1191 by a duke whose name I will not mention as you will forget it anyway. In later years you come across historians who tell you that even before that year there had been a settlement in that place, and that 1191 is only the date when the settlement was enlarged.

The same uncertainty can be noted concerning the name. It is said that the city was named by the above-not-mentioned duke after the first animal he killed on the spot: a bear. So Berne is the city of the bear. It could also be the Germanized Italian place-name Verona; however, let's not waste time on this insignificant problem!

By the way: we spell it Berne, and the pronunciation is not "burn," but "bairn." So if you want to impress the Bernese, try to pronounce the name properly. If you fail, never mind—we have the same troubles with American names. You will not find many Bernese who have the correct pronunciation of names like "Mojave," "La Jolla" and "Houston."

When Berne was founded, Switzerland did not yet exist. Only one hundred years later the three original cantons in what is now known as Central Switzerland concluded a pact—that was the William Tell area, you know—and initiated a confederation of states which, at the end, united 22 states. We call them cantons.

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*The only non-medical author in this issue, is known throughout Switzerland as the Bernese contributor to the "Nebelspalter", the Swiss equivalent of "Punch". He is also the author of several very popular books about Berne and the Bernese, the unique character of which will—we trust—be obvious to our American colleagues having read his introduction. P. Lundsgaard-Hansen, M.D.

The canton of Berne, then a republic, joined the Confederation in 1353. Soon it became obvious that Berne, a mighty and thriving city, had the wisest statesmen and the best military leaders and was therefore predestined to take the helm of the young nation which, at that time, was not a real nation but just a loose organization of independent cantons with some common interests and many common enemies.

Now let us skip about four centuries and open the history book at the chapter dealing with the French Revolution and its consequences. The revolutionary ideas had also taken root in Switzerland and arrayed the governed classes against the governing class. It was a most unpleasant time, with crowds shouting "To the gallows with the aristocrats!" and, therefore, when Napoleon's armies invaded Switzerland in 1798 they did not meet much resistance because the Swiss were weakened by inner strife. So, for the first time in history, the proud city of Berne was occupied by an enemy. Besides the freedom of the citizens the French also took away their arms, their watches and the state treasure, which did not make them very popular; but in later times the Bernese regained most of the money by exploiting French tourists. Crime never pays.

Napoleon tried to give Switzerland a new constitution. His various experiments were not very successful, and later he had to give them up entirely because he was too far away, exiled to the small island of St. Helena. The Swiss did not miss him much and now tried themselves to find a new way of coexistence. The constitution of 1848 finally established national unity and made of the former Confederation of States a Federated State. This constitution, totally revised in 1874, is still effective today.

In the same year—1848—the newly created National Council ("House of Representatives") and the Council of States ("Senate") had to choose the seat of government. Zurich, Berne, Lucerne and a few minor cities claimed it. Berne got it. Why?

Because of Berne's centuries-old leading role in Swiss politics, because of the most substantial contribution of Bernese statesmen in drawing up the constitution, and because of its geographical location near the border-line between the French and the German-speaking parts and its importance as a mediator between two cultural components.

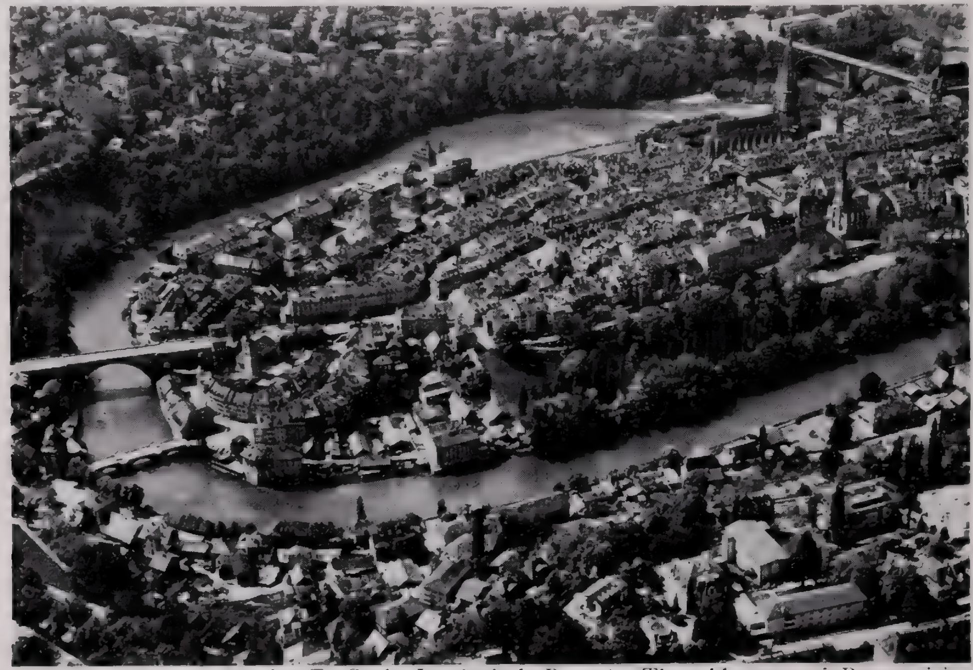

Fig. 1—(Photograph by E. Grob, Inselspital, Berne). The old town of Berne rising above the bend of the river Aare, viewed from the North. The longitudinal axis is formed by the main street terminating onto the Nydegg bridge, to the left of which (outside the picture) the Rose Gardens and the Bear pits are sited. The transverse axis links the Cathedral with the ancient Town Hall beneath its heavy roof, flanked by the Old Catholic Church.

The result of that vote naturally meant a great honor to Berne, but also a considerable burden for a city of then some 26,000 inhabitants who now had to provide the necessary buildings for the central government.

The costly Parliament Building was inaugurated on June 5, 1857. Our great-grandfathers paid for it.

A Living Monument

Berne differs from all other cities claiming to be the loveliest in the world in that it *is* the loveliest.

You may suspect me of boasting now. If you have never been here, I can understand. But if you have ever looked down from the Rose Gardens—a public park—onto the old part of Berne, you will share my feelings, unless your idea of urban beauty is closely connected with concrete and steel constructions, neon lights and noisy traffic.

The View from the Rose Gardens

A peninsula is formed by a wide bend of the river Aare which, coming from the Bernese Oberland, decided here to change its course but found the place so lovely that it formed several loops before departing towards the Jura Mountains, the Rhine and the sea.

The Old Town

This half-island—seen on Figure 1—rises some 120 feet above the river and contains what we call the Old Town. The broad and sunny main street curves gently down through its center, accompanied by somewhat narrower side-streets, all of them converging near the vertex of the river bend. At this point there used to be a ferry, the only place to cross the Aare until the beginning of the 13th century.

What makes the Old Town so charming and unique is the fact that here a medieval town has preserved its original character without becoming a lifeless museum or a mere showpiece for tourists. The narrow gray sandstone houses huddled together to form large, irregular blocks mostly date from the 18th century, but the layout of the streets is still the same as it was 800 years ago. The city planners of 1191 must have been very farsighted, for the width of the main street—80 feet—is the same as of New York's Fifth Avenue, which was built considerably later. And this antique part of the Swiss capital is, as I have already said, by no means a museum, but on its ground level a thriving shopping center and in its upper regions a favorite residential section interspersed with offices of all kinds.

The Arcades

This is the moment to say a word about the arcades. You must know that Berne, from its origin, was a market town. It had no specific market place; the farmers from the surroundings sold their produce in the streets. At the beginning arcades projecting into the streets gave them shelter; later the arcades became an integrated part of the sandstone houses occupying the front of their ground floor and were mainly used by craftsmen who liked to work outdoors, and today they have become a public thoroughfare serving as sidewalks—but what sidewalks! Just take a leisurely stroll through the approximately five miles of Bernese arcades. Never mind the weather—you are sheltered from rain and snow as well as from extreme heat. Look at the varied styles of their vaulting and pillars, at the wood and stone benches under the arches and realize that you are enjoying a prerogative dating back to imperial times: the right to walk on private ground which must be maintained by the house owners.

The main street arcades are lined with restaurants and shops of every kind and price category, from modern supermarkets to old-fashioned antique shops. In the arcades of the side-streets you will admire the beautifully carved doors of private homes with knockers beside electric bells, and in certain places you can still see craftsmen at work.

Knockers and Electric Bells

Knockers and electric bells: this is a good symbol for our Old Town. We preserve the old without refusing the new. For you must not think that life in these medieval looking houses is medieval; once you have opened the heavy door and climbed up a spiral staircase—if you do not prefer to take the elevator—you will find apartments offering you every comfort. It is not forbidden to modernize the interior of

Old Town buildings; only the renovation of the exterior is subject to very rigid regulations, because the city authorities are determined to protect the beauty of Old Berne, and the Bernese voters who adopted those regulations agree with them.

Other Tourist Attractions

There is one danger threatening all sightseers in Berne: they are often so absorbed in enjoying the arcades that they miss the other architectural and artistic beauties of the city. So if you ever come to Berne don't forget to step into the street from time to time. You will, for instance, discover that the Bernese are passionate flower lovers. They applied flower power long before the Hippie era by decorating their windows with thousands and thousands of geraniums. You will also chance upon some most admirable fountains with sculptured figures: a town messenger, a flag-bearer, a marksman, a bagpiper, an ogre, a woman personifying justice—to mention only a few of these world-famous fountains mostly dating back to the 16th century.

Clock Tower

Speaking of world-famous sights we must

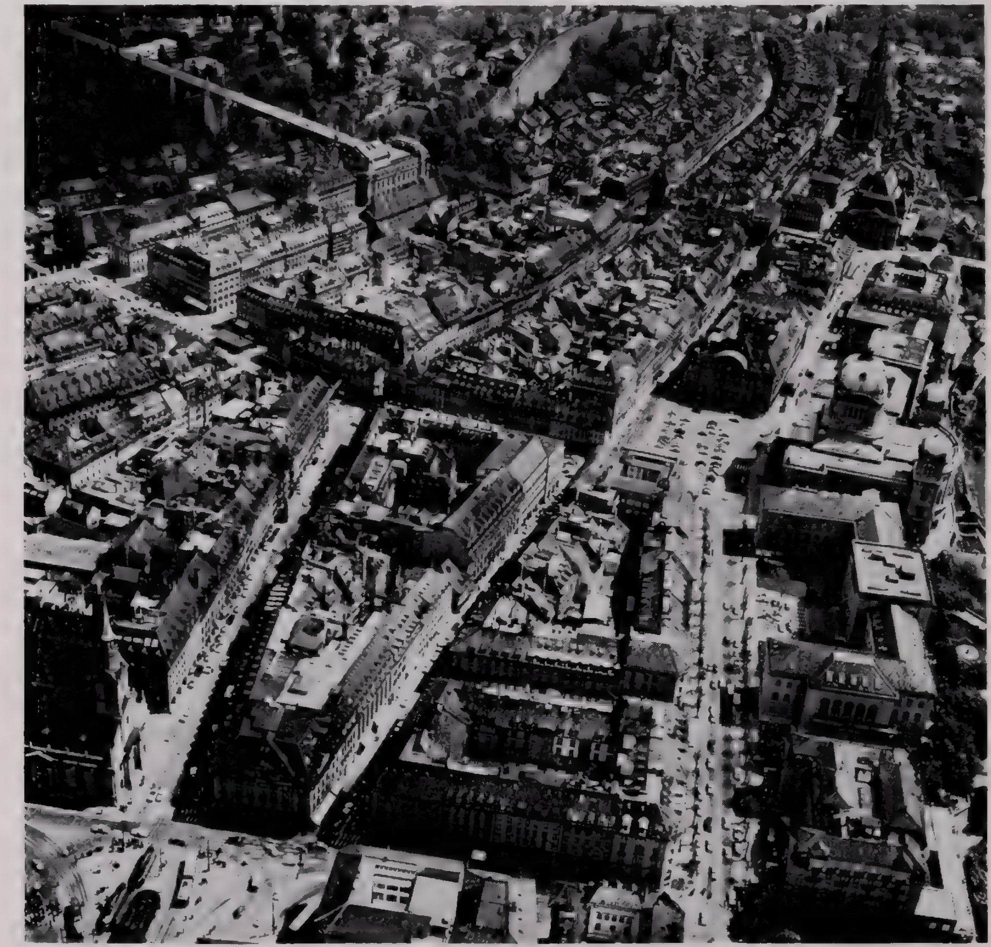

Fig. 2—(Photograph by E. Grob, Inselspital, Berne). Air view of the center of Berne seen from the West. Lower left corner: Central Railway Station Square. Taking the main street past the baroque church of the Holy Spirit, the reader arrives at the Prison Tower and, proceeding further, at the famous Clock Tower. From there he may go on towards the top of the picture, with the Cathedral on his right hand, and reach the Nydegg bridge (upper margin of picture). Crossing that bridge, he will arrive at the Bear Pits. Proceeding along the second street departing from the Railway Station Square, the visitor reaches Parliament Square with the Federal Palace under its dome, flanked by the Federal Administration buildings.

The Inselspital (University Hospital) is located some ¾ of a mile west of the Railway Station Square.

not forget the Clock Tower, probably the most photographed object of Berne. It is one of the two gate-towers marking the growth of the city (the other, some 300 yards farther west, being the Prison Tower). Its most remarkable features are a figure-play and a calendar clock which were constructed in 1530. Every full hour Father Time, turning an hourglass, a crowing rooster, a jester and a procession of little bears make a crowd of camera-equipped tourists scream with delight. Even the Bernese stop sometimes at that corner and enjoy the display of an ingenious mechanism more than 400 years old.

Bear Pits

Another "must" for foreign visitors are the Bear Pits. You will find them when you walk down the main street and cross the river on the Nydegg bridge (completed 1844). Immediately after crossing the bridge turn right and you are at the place where we keep our beloved heraldic animals. These amiable creatures perform all kinds of tricks to obtain a carrot or a fig or some other fruit, and the young ones, of course, are just darlings!

Cathedral

The most outstanding building in the old section is the Cathedral. Its first stone was laid in 1421; about a century later its main body—all made of sandstone—was completed; but the tower, the highest in Switzerland, did not reach its present height until 1893. Stained-glass windows and choir stalls carved out of oak wood deserve a closer look, and the Last Judgement sculpture above the main portal containing 238 individual figures is one of the country's most valued art treasures.

By the way: the Cathedral is a Protestant church. About 77 percent of the 170,000 inhabitants of Berne are Protestants, 21 percent Roman Catholics.

As it is not my intention to give you a lecture on the history of Bernese art and architecture, I just mention that we have also a Town Hall and many other public buildings deserving your attention—not to forget the Parliament Building (Federal Palace, as we call it patriotically) and the many other structures humming with federal, cantonal and municipal officials.

A Modern City

Once you have left the arcades you will discover that not everything in Bern is made of sandstone. High bridges span the Aare valley and connect the Old Town with green residential districts, and towards the west the city expands with new business streets and modern settlements which attract city planners from all over the world as they demonstrate that great numbers of families can live close together without losing their privacy and contact with nature, or, if I may put it this way, that giving up Beverly Hills does not necessarily mean Manhattan.

In industrial areas at the outskirts not only chemical products and chocolate and other foodstuffs are made, but also electronic equipment, printing presses and other such high precision machinery important for export.

Education and Culture

From kindergarten to university all opportunities to acquire a good education are offered in Berne. Museums—among them the world-famous Museum of Natural History—and libraries are abundant. Concerts are always sold out, and beside the venerable Municipal Theater we have also a number of "underground stages" established in large cellars of the Old Town where experimental plays and cabaret performances are given.

Famous names of outstanding writers, artists and scientists are closely connected with Berne. I mention only Albert Einstein who, in the peaceful atmosphere of the Old Town, worked on his theory of relativity, and James Fenimore Cooper who spent the summer of 1828 in Berne while writing his Leather-Stocking Tales.

In one special field Berne is leading in Switzerland: dialect theater. You must know that High German is not our native language; like all other cities and regions in Switzerland we have our own local dialect, the Bernese, and High German has to be learned at school before we are able to read books and write letters.

Now the Bernese are so fond of their mother tongue that they preserve it like their

Old Town. In no other Swiss region are there as many dialect poets and writers and dramatists as in the capital, and Bernese radio plays are very popular all over the country. The same love of native culture applies to costumes and folklore and yodeling; but if you expect to hear yodels under the arcades you will be disappointed, for this audible display of happiness would be incompatible with the Bernese mind.

The Bernese Mind

If you ask the Swiss from other cantons what they think of their Bernese confederates they are likely to answer: "Oh well, they are certainly very industrious and efficient and reliable, but awfully slow and dull."

If you believe this, you are the deplorable victim of a most unfair misinterpretation of our general behavior.

It is true that, compared with Italians or Mexicans, the Bernese are somewhat less extraverted. They do not dramatize their feelings; they often do not even show them.

Should this composure lead to the conclusion that they are dull? Knowing the Bernese I can assure you that this would be extremely wrong. Among themselves, in their families or with friends they can be very cheerful and witty. Their sense of humor is well developed, and their jokes are full of irony, both philosophical and self-directed, but never offensive. They are warm-hearted without being sentimental, gay without being frivolous.

Now what about their alleged slowness? Our critics pretend that the rather low speed of our speech originates from mental slowness. They base this theory on the completely erroneous idea that a person's intellect and imagination can be measured by the number of syllables produced by his speech organs per minute. I maintain on the contrary that those who speak very fast cannot think over what they are saying. So this so-called Bernese slowness is in fact a sign of wise consideration: no word leaves the mouth unless it is well considered.

History has proved that this reluctance to say or do anything before it has matured in the mind is one of the best Bernese qualities. Thanks to this attitude the State of Berne has steadily grown through the centuries and united French-speaking Switzerland with German-speaking Switzerland; thanks to it revolutions and strikes are unknown here, and thanks to it the Bernese is always as good as his word.

Some say that we are unsociable. We certainly do not jump at every stranger, telling him our private story within the first five minutes, but we welcome every visitor who comes to Berne, and once we have made sure that he is neither a criminal nor a silly prattler he will soon realize that our hospitality is sincere and our friendship reliable.

A Final Word

Rereading what I have written I fear that you get a wrong impression of the Bernese. While everything I said about the beauty of the city is absolutely correct, my passionate love of Berne may have carried me away into shameless bragging. Sorry! Believe me, the Bernese are modest and unpretentious. We are not the Texans of Switzerland, although our state is, like Texas, the second largest of the country. We are proud of Berne, the Queen of Swiss cities, but we show our pride only on very rare occasions.

This article is one of them.

Placebo Diagnosis

Partly because most patients so demand a diagnosis of organic disease, partly because they are inclined to be resentful against the physician who tells them the truth, and partly because it takes so much time and skill and tact to explain the real situation to them, we physicians will always be tempted to dismiss them quickly with some placebo diagnosis—some pleasant-sounding name such as clitis, ptosis, spastic colon, low blood sugar, or low blood pressure.*

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*W. C. Alvarez in Richard Magraw: Ferment in Medicine, 1966.

To write prescriptions is easy, but to come to an understanding with people is hard.—Franz Kafka

History of Medicine

The Inselspital Berne

F. KOHLER, M.D.*
Berne, Switzerland

THE INSELSPITAL was established in 1354 by a wealthy woman of the city of Berne, Anna Seiler, in form of a foundation. This foundation was provided with a house, situated in the middle of the old town of Berne, as well as with the revenues of important land-property. The donor put the hospital, soon known as "Seilerin-Spital", under the custody and the protection of the Town-Mayor and his Counsel henceforth all through the centuries. The Inselspital has maintained the character of the foundation in spite of historical and political changes, still being an independent foundation, based on the deed of foundation of Anna Seiler, subordinate to the regulations of the Swiss Civil Code and—as to its public duties—to cantonal law.

The Seilerin-Spital

In 1528 the Seilerin-Spital moved into the premises of the Insel-Cloister which, as a result of the reformation, was unoccupied and which was formerly situated on a little island in the river Aare. From this time on the hospital has been called "Inselspital".

In 1724 a new building was set in operation at the place where the Swiss House of Parliament is situated today; but having no possibility of extension the place was left in 1884 to move into the newly-built hospital-establishment with a capacity of 320 beds (a hundred beds more than in the former building), situated outside the town. In those days this new hospital was said to be a perfect example of good hospital architecture.

The Inselspital, initially installed for "13 bedridden, poor persons", developed more and more into the central hospital of the Canton, viz., the Cantonal Hospital. Since 1805, when under the auspices of the Academy a Medical Faculty was organized, the Inselspital has the function of University-Hospital as well. In 1834, the year of the foundation of the University of Berne, the Inselspital consisted of two departments with 44 beds. Today the teaching departments have nearly 730 beds and the non-teaching departments, roughly 400 beds.

The Inselspital

Thanks to the erection of the "Anna Seiler-Haus" set in operation in 1954 and comprising 190 beds, and owing to the thorough renovation of the C. L. Lory-Haus (about 150 beds) in 1956-57, the Inselspital constituted well-equipped non-teaching divisions which, for ancient legal reasons, are not open for teaching and research-purposes. The teaching divisions, however,

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*Director, Hospital, Berne, Switzerland.

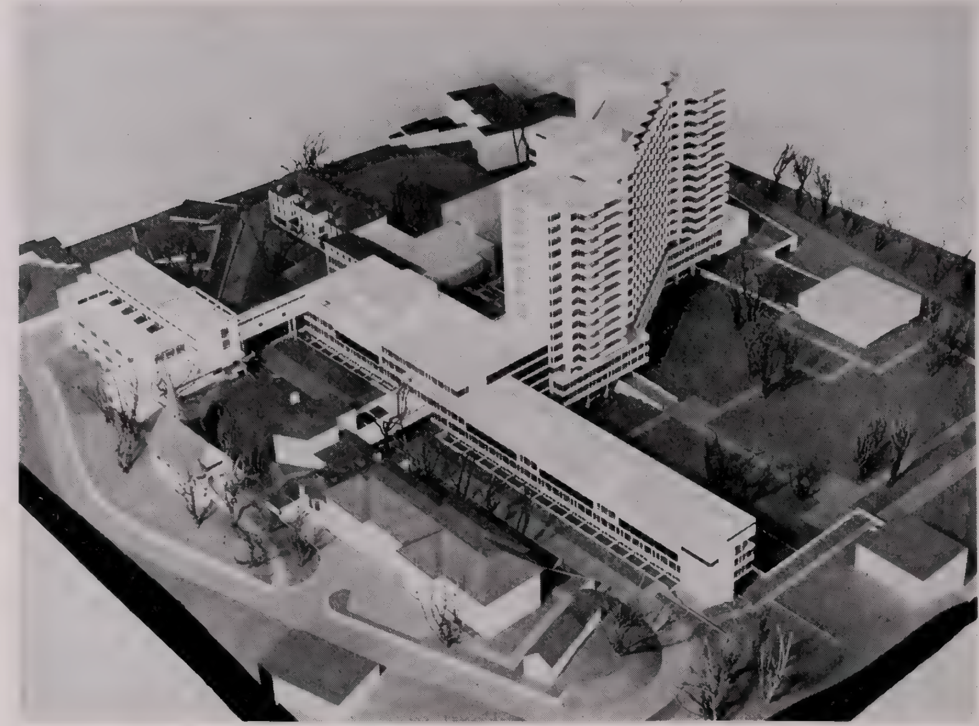

Fig. 1—Model of the new buildings 1960-1970. Ward block with the long diagnostic and treatment-building in the foreground. In the lower left the kitchen-building with kitchen, laundry, cafeteria.

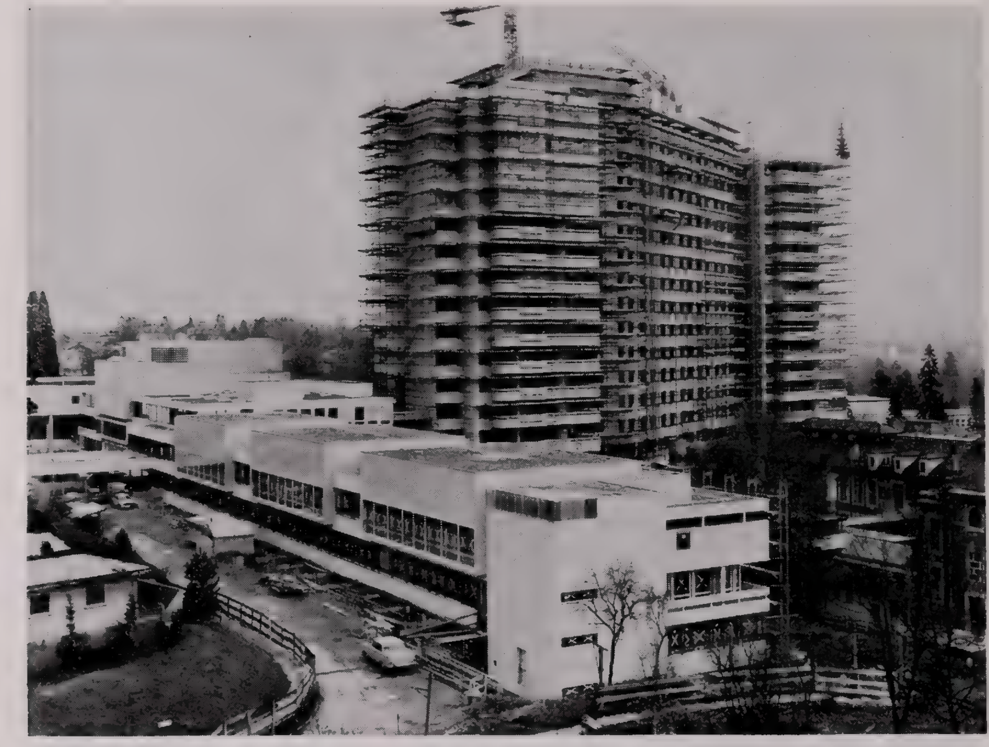

Fig. 2—The ward block is under roof (November 1967). In the foreground is the diagnostic and treatment-building, its left side having been completed in 1964.

were lodged for the most part in houses built in 1883 and 1884, representing the pavillion-type, which no longer met the standards of a modern Cantonal- and University Hospital. Thanks to the foresight of the cantonal architect it was decided in 1955 to study possible reorganization of the oldest buildings. Dr. H. C. R. Steiger, Zurich architect, was entrusted with this task, and he concluded that all the centrally situated old buildings should be razed and replaced by connected buildings forming a compromise between the one-block hospital and the pavillion-type. In the course of the following planning-period the architects Drs. Fietz and Steiger, Zurich, Brechbühl and Itten, Berne, arrived at the solution shown in Figure 1.

The total renewal of the hospital, for which a credit of 69 million Swiss francs was granted in 1958, is to be executed in three phases. After phase one it appeared that this amount would not be sufficient for a building-project of such a dimension, as the first phase—completed in 1964—had required 40 million Swiss francs. This first portion comprised the following buildings: a house for personnel; a house for nurses; a building for economic branches, with central kitchen, laundry, cafeteria for the staff; one half of the diagnostic and treatment building; and the roads, underground links, water- and power-supply for all three phases.

For the second phase the Bernese electors granted a further credit of 87.8 million Swiss francs in September 1964, including: a ward-block equipped with about 730 beds, to be occupied in 1970 (length 101 m; height 71 m) (Figure 2), and the second part of the diagnostic and treatment building, ready for use in 1969. This last mentioned building will include: an emergency department, a ward for sick prisoners, the hematological and chemical central laboratories, a diagnostic X-ray department, an X-ray therapy division, a central sterile department, and nine operating theatres.

However, there are no plans as yet for the third phase of the total renewal of the Inselspital.

Increasing Costs

The increase of old-aged people, the developments in therapy and diagnostics as well as in surgical operations, the terrific augmentation of street-accidents and last but not least, the greater trend towards hospitalization (partly due to the lack of home nurses and as a result of restricted lodging possibilities) have led to the turbulent development of the Inselspital during the years after the war. This development may be stated by the following figures:

Year	Number of patients	Number of patient-days	Number of personnel	Cost per day and patient
1940	8,384	228,818	306	8.107
1950	9,473	241,202	494	17.248
1960	12,049	303,864	948	37.984
1966	15,959	349,356	1,820	89.33

The impressive increase in the personnel sector is especially noteworthy, the number of staff within about six years having nearly doubled and the costs nearly trebled. Nobody is any longer wondering about Cantonal and University Hospitals showing big deficits; it is evident that patients in the general ward never will be able to pay the above-mentioned costs. Consequently the hospital has to meet a social obligation by assessing moderate daily rates for care and treatment. As a matter of fact the Bernese citizen, supported by the social-authorities, still enjoys today the favor of being hospitalized free of charge at the Inselspital.

Service to the Community

The Inselspital is an institution which—owing to a highly specialized staff and special medical equipment—is able to receive the most exceptional and critical cases, besides being a center for teaching and research. The teaching of medicine and the education of young doctors prevail, but the following schools governed by the Inselspital deserve to be mentioned: the school for physiotherapists, the school for laboratory technicians, the school for auxiliary nurses, and the school for nurses for chronic sick and aged persons (practical nurses).

Besides being a place where cooks can serve their apprenticeship, the hospital facilities are all the more in demand for the practical education of future house-keeping-officers and social workers. In this way the Inselspital further serves the population of our Canton, as stipulated by Anna Seiler more than 600 years ago.

SHAKESPEARE'S DOCTORS

Cerimon

" 'Tis known, I ever
Have studied physic, through which secret art,
By turning o'er authorities I have,
Together with my practice, made familiar
To me and to my aid the blest infusions
That dwell in vegetives, in metal stones;
And I can speak of the disturbances
That nature works, and of her cures; which doth give me
A more content in course of true delight
Than to be thirsty after tottering honor,
Or tie my treasure up in silken bags,
To please the fool and death." (Pericles III, 2)

Scornful of hollow prestige and venality, thus spoke Cerimon when his friends expressed surprise that he, a nobleman, should show an interest and some skill in medicine. While only an amateur rather than a certified physician, he fully qualifies as one of Shakespeare's doctors, acquitting himself as ably as any.

When a chest containing the "corpse" of Thaisa is cast ashore from a shipwreck off the coast of Ephesus and is opened, Cerimon immediately detects that the body within shows faint signs of life and sets about to revive it.

"For look how fresh she looks! Make a fire within:
Fetch hither all my boxes in my closet.
Death may usurp on nature many hours,
And yet the fire of life kindle again
The o'erpressed spirits.
The fire and cloths.
The music there! I pray you, give her air." (Pericles III, 3)

Cerimon's armamentarium consisted of warm packs, fresh air, stimulating music, and unidentified substances from his boxes, presumably stimulants.

Industrial and Forensic Medicine

Organic Solvents in Blood

Determining the Quantity

ORGANIC SOLVENTS are becoming ever more widespread at work and in the home. This means that the number of solvent intoxications will increase still further.

Although the effects of individual organic solvents on the organism have been studied thoroughly, little attention has been given to quantitative determination in blood and organs. It is true that in certain cases it was possible to explain the often relatively uncharacteristic, pathological-anatomical picture by means of chemical detection of the poison; however, for this purpose relatively large quantities of blood or organs had to be processed in order to detect the solvents that were present only in traces. Also, since the appropriate chemical methods were frequently lacking, the poison could in many cases be detected only indirectly by examination of the work premises or the accident site. This procedure may to some extent suffice for a plausible clarification of a simple case, but in complex cases such an indirect procedure, even if possible, often gives too limited or too inconclusive, unsatisfactory results. Hence legal, insurance, or industrial health questions could not always be answered satisfactorily.

Gas Chromatography

Because of its high sensitivity, gas chromatography permits the determination of small traces of organic solvents; therefore, it seemed to us a suitable method for solving the problem under discussion here. We investigated the technical possibilities and developed in our Institute a procedure which enables solvent traces to be detected in small blood samples. The procedure consists of injecting ten microlitres of whole blood without further preparation straight into the gas chromatograph. Where apparatus conditions are suitable it is even possible by this method to determine volatile physiological substances in their normal concentrations. To do this, however, one needs a special sample inlet which retains the high-boiling blood components and also a water-resistant high-efficiency column.

We designed the sample inlet in the shape of a quickly exchangeable cartridge which can be attached to the chromatograph with a gas-tight bayonet fitting. Changing and heating this cartridge takes only about a minute, thus facilitating rapid, reproducible work. We avoided another considerable difficulty—coagulation of the blood in the needle of the liquid sampler—by an additional cooling of the inlet septum.[1]

To begin with we had the commercially produced stationary phases and solid supports for the construction of the column. Three requirements for the columns severely limited the number of possible liquid phases; these were water resistance of the stationary phase, complete separation of the trace substances from the main mass of water, and the best possible resolution of the organic trace elements.

Practically speaking there remained only Carbowax, Chromosorb 102 and Porapak. In the case of Carbowax either the separation of the water or the resolution of the trace substances is unsatisfactory. The two other materials (polystyrene derivatives) separate the water very well, but detection of tiniest solvent traces is difficult as many technical solvents are only slightly polar and consequently can be eluted* only at high temperatures as relatively flat peaks, making analysis considerably more difficult.

For these reasons we synthesized (made to measure, as it were) a stationary phase for the gas chromatography. From a technical and theoretical point of view good results can be expected from a material with the following characteristics: high hydrophilic group content to separate the water from the organic components; enough hydrophobic groups of different structure to separate lipophilic organic substances; chemical resistance to water at high temperature and pressure and to a very large contact surface (very thin film on active solid support), for which reason only the use of water-resistant C-C and C-O-C (ether) bondings was suitable for our purposes. Finally, low volatility is required, so that the bleeding of the column remains relatively small, or so that tiny traces of an organic solvent can actually be detected in the background. The substance therefore has to have a relatively high molecular weight.

From these considerations we coupled relatively hydrophobic alkylphenols with the hydrophilic glycerine, using ether bondings. The high separations

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*See Test Your Word Score Page 89.

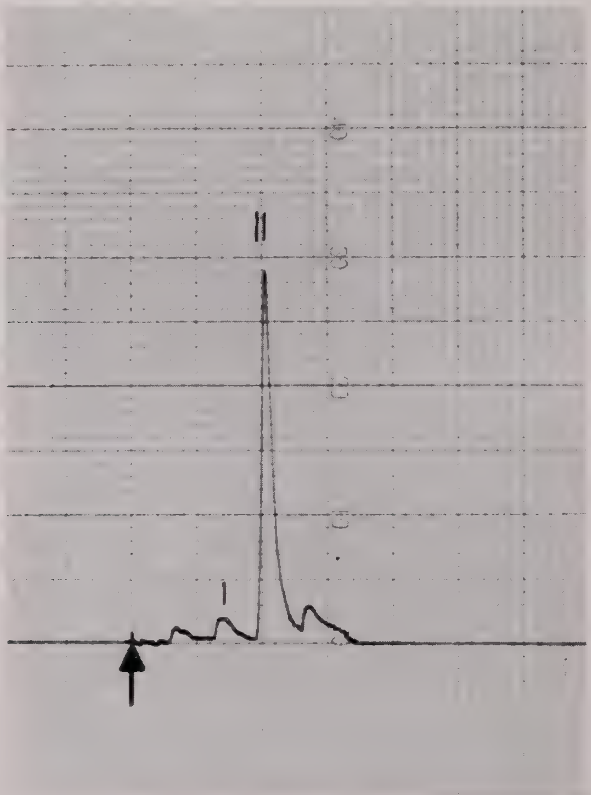

Fig. 1—Whole blood (rat). I = acetaldehyde. II = acetone.

of greatly diluted watery solutions achieved with these materials[2,3,4] subsequently confirmed our theoretical suppositions. For the time being the following proved to be the most suitable column[5] (at present being further developed): 12 feet, 3/16″, stainless steel, with 10% of a mixture of 78 parts NPGA and 22 parts ORGA on Chromosorb A, 60/80 mesh.

This resolves the technical solvents to a large extent. The chromatographed substances are eluted roughly according to their boiling points, thus making identification of the fractions considerably easier.

Clinical Application

To illustrate the analyses possible with this method we present some examples from our practical work.

Control of Physiological Substances in the Blood

Figure 1 shows a gas-chromatogram of normal rat blood, two of the peaks representing the acetaldehyde or acetone in the physiological range (ppm-range). This method is therefore also suitable for dealing with problems of metabolism. Tests in this connection are at present being carried out at our Institute.

Detection of Gasoline Intoxications

Gasoline fractions, as largely inert hydrocarbons with conventional chemical reactions, are practically impossible to detect in the micro-range, and, for this reason their detection in blood had previously been impossible. But

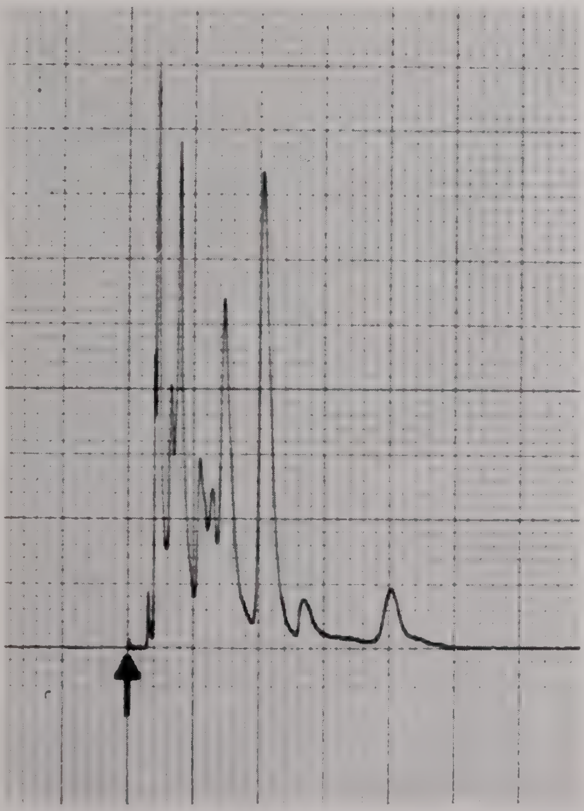

Fig. 2—Whole blood of a rat intoxicated with gasoline.

gas-chromatography solved the problem; by its application about fifteen hydrocarbon fractions, all contained in inhaled gasoline, were detected in the blood of a worker (Figure 2).

These results have been checked experimentally in animal tests when a lethal gasoline concentration (total of all fractions) of only 0.3 – 0.4 o/oo was ascertained.[6] The concentration of individual subfractions was, of course, much lower, ranging from only a few up to about fifty ppm.

Detection of Solvents in the Case of a (Compulsive) "Sniffer"

The blood of a fifteen-year-old boy was also examined by gas-chromatography because of repeated fits of intoxication and raving madness. The analysis revealed not only increased acetone concentration but also considerable amounts of chloroform, carbon tetrachloride and ethanol solvents, contained in a stain-removing preparation.

Detection of an Intoxication Caused by Paint Thinner

A young man was found dead in a storeroom for empty solvent containers. Initially the cause of death was not clear, but gas-chromatography subsequently revealed a number of solvents in the dead man's blood. They were:

0.1 o/oo	toluene
1.2 o/oo	isopropanol
1.0 o/oo	methyl-ethylketone
0.3 o/oo	methyl-isobutylketone and
0.8 o/oo	acetone

All these substances were contained in a so-called nitro-thinner, some of which was later found in a container, thus identifying the source of the poison. Whether the intoxication was due to chance exposure or to addiction could not be clarified.

We believe that these few examples clearly indicate the advantages of gas-chromatography for toxicological determination of organic solvents in the blood. With increasing experience the quantitative determination of the poisonous substances will permit an approximate estimate of the seriousness of such intoxications.

Summary

With suitable modification, gas-chromatography can be used for direct qualitative and quantitative determination of organic solvents in blood. A number of typical cases from our practical experience show that non-lethal or even physiological concentrations can also be established.

U. P. Schlunegger
Berne, Switzerland

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*Institute of Forensic Medicine, University of Berne, Switzerland.
(Director: Prof. E. Läuppi)

We should like to express our sincere thanks to the Foundation for the Promotion of Scientific Research at the University of Berne for the support it has given to the present project.

References may be secured from the author.

There is no pleasure in having nothing to do; the fun is in having lots to do and not doing it.—Mary Wilson Little

The Question in Life

There's always a big "if" in the center of life.—Consol Dealer

Laboratory Letter

Chemistry Graphs in Liver Diseases

As a measure of liver function, chemistry graphs excel. Of the twelve tests on the graph, seven—albumin, alkaline phosphatase, total bilirubin, cholesterol, SGOT, LDH, and total protein—relate in some way to the liver.

Among diseases of organ systems, few are tougher to define precisely than those of the liver. Sometimes, even after a good history, a thorough physical, x-ray studies, and a host of laboratory tests, the diagnosis still remains in doubt. Yet with certain diseases, a chemistry graph gives solid clues as to the nature of the liver process. Here are a few examples of uncommon disorders in which we have been able to help the physician interpret the graph.

Alcoholic Hepatitis

What is alcoholic hepatitis? Probably the condition that precedes portal cirrhosis. Histologically, the liver shows focal necrosis and polymorphonuclear leucocyte influx. Yet patients often do not have symptoms, though they may complain of anorexia, nausea, vomiting, and abdominal pain that can mimic cholecystitis, pancreatitis, or even appendicitis. Also they sometimes have fever and leucocytosis. Most liver function tests are normal, but the SGOT is often up in the range of 50 to 200 units. If patients drink excessively and have an unexplained SGOT elevation, most will usually show changes of alcoholic hepatitis on liver biopsy.

Subacute Hepatitis

What do you do when a non-drinking patient has the clinical picture of portal cirrhosis? Chances are, you question whether the history is valid. Yet when the patient is a middle-aged woman, it is worthwhile to consider subacute hepatitis. This disease, a sequel of viral hepatitis, smoulders for months or years and culminates in postnecrotic cirrhosis. It has a striking predilection for women over 40 (about 90% of cases). Though ultimately the diagnosis is histological, certain clinical features—intense or protracted jaundice for months or years, or signs and symptoms of liver destruction in an otherwise typical viral hepatitis—ought to make the physician seriously consider subacute hepatitis. Chemistry graphs can give you information—elevation of serum transaminase for months, a striking fall in albumin levels, and a persistent hyperglobulinemia—that you rarely see in benign hepatitis.

Biliary Cirrhosis

Though some claim that this is merely a variant of posthepatitic cirrhosis patients with "biliary cirrhosis" do have characteristic clinical features—chronic itching, insidious jaundice, xanthomas, large livers, and a predominance of women. On the chemistry graph, total bilirubin, alkaline phosphatase, and cholesterol are moderately to strikingly elevated, but other liver function tests remain normal until late in the disease. A new hypocholesteremic agent, cholestyramine, which binds bile acids in the intestine, often relieves pruritis.

These, then, are a few conditions in which chemistry graphs offer helpful information. For brevity's sake, we have not mentioned changes found in portal cirrhosis, viral hepatitis, fatty metamorphosis, infection mononucleosis, "lupoid" hepatitis, drug cholestasis, extrabiliary obstruction, and metastasis to the liver, although all may give recognizable patterns.

Richard L. Reece, M.D.
Minneapolis, Minnesota

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IN BRIEF.

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Precautions: Keep out of reach of children. Not recommended for patients 12 years old or less. Carefully supervise dose and amounts prescribed, especially for patients prone to overdose themselves. Excessive prolonged use of meprobamate in susceptible persons—as alcoholics, ex-addicts, severe psychoneurotics—has resulted in dependence or habituation. Withdraw gradually after prolonged excessive dosage to avoid possibly severe withdrawal reactions including epileptiform seizures. Warn patients of possible reduced alcohol tolerance, with resultant slowed reactions and impaired judgment and coordination. If drowsiness, ataxia or visual disturbances (impairment of accommodation and visual acuity) occur, reduce dose. If symptoms persist, patients should not operate machinery or drive. After meprobamate overdose, prompt sleep, reduction of blood pressure, pulse and respiratory rates to basal levels, and hyperventilation are reported. Give cautiously and in small amounts to patients with suicidal tendencies. Treat attempted suicide (has resulted in coma, shock, vasomotor and respiratory collapse and anuria) with gastric lavage and appropriate symptomatic therapy (CNS stimulants and pressor amines as indicated). Two instances of accidental or intentional significant overdosage with ethoheptazine and aspirin have been reported. These were accompanied by CNS depression (drowsiness and lightheadedness) but resulted in uneventful recovery. On basis of pharmacologic data, CNS stimulation could be anticipated, with nausea, vomiting and salicylate intoxication (requires induced vomiting or gastric lavage, specific parenteral electrolyte therapy for ketoacidosis and dehydration, and observation for hypoprothrombinemic hemorrhage [usually requires whole blood transfusions]).

Adverse Reactions: Ethoheptazine and aspirin may cause nausea with or without vomiting and epigastric distress, in a small percentage of patients. Dizziness is rare at recommended dosage. Meprobamate may cause drowsiness, ataxia and rarely allergic or idiosyncratic reactions. These reactions, sometimes severe, can develop in patients receiving only 1 to 4 doses. Such patients may have had no previous contact with meprobamate and may or may not have an allergic history. Mild reactions are characterized by urticarial or erythematous maculopapular rash. Acute nonthrombocytopenic purpura with cutaneous petechiae, ecchymoses, peripheral edema and fever have been reported. If allergic reaction occurs, discontinue meprobamate; do not reinstitute. Severe reactions, observed very rarely, include fever, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (1 fatal case), anaphylaxis, stomatitis and proctitis (1 case) and hyperthermia. These cases should be treated symptomatically including, when indicated, such medication as epinephrine, antihistamine and possibly hydrocortisone. A few cases of leukopenia, usually transient, have been reported on continuous use. Rarely, aplastic anemia (1 fatal case), thrombocytopenic purpura, agranulocytosis, and hemolytic anemia have been reported, almost always in presence of known toxic agents.

Overdosage: See precautions section for management of overdosage.

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(Continued to page 200)

Law and Medicine

Procurement of Transplantable Tissues

THE NEED FOR transplantable tissues has grown enormously in the 20th Century. Through the years man has made many attempts to transplant various tissues and organs from animals and other men,[1] but it was not until 1900, when Landsteiner described the blood groups in man, that the success of blood "transplants" or tranfusions became feasible. These observations not only laid the ground for transfusion therapy, but opened the entire field of tissue transplantation.[2] The state of blood tranfusion as a routine safe procedure today is the goal for organ transplantation in the remainder of this century. To realize this goal, advances are needed in techniques in understanding and control of the rejection process, in organ preservation, and in moral and legal areas so that this new knowledge can be applied more promptly.

Source of Tissue

The sources of transplantable tissues are three: Living donors (related or non-related), cadaver "donors" and animal donors. At present, the best results with organ transplantation have been with kidneys taken from blood-related donors of compatible blood types.[3] It is in this group also that the moral and legal questions have been the least problem since the donor is able to willfully donate his kidneys. Unfortunately, the use of the blood-related living donor is limited to those who have such a suitable donor and those who require only the transplantation of expendable tissues such as blood or kidney. Fortunately, no living donor has died at operation, nor have any needed their previously donated organ. Sooner or later, however, this problem will occur.

The use of animal donors, while an attractive solution, has not yet been successful for any length of time.[4,5] When the immunology of transplantation is more advanced, animals might be the ideal source for tissues. This will eliminate the moral and legal issue of jeopardizing the life of the donor to prolong the life of the recipient. Also, since the animal is expendable, the transplantation will be scheduled at the convenience of the patient and his physicians.

At present, the human cadaver serves as the only practical source for many organs. Couch classifies cadaver tissues into two groups:[6] Critical tissues are those whose usefulness depends upon their viability, but whose viability is lost so rapidly at normal temperatures that postmortem legal procedures, tissue procurement and transplantation must be completed in a matter of minutes. In this group are the kidney, liver, heart, lung, pancreas, intestine, and most other organs; non-critical tissues are those that can be removed at leisure after death. They are subclassified into two types: viable, such as skin and cornea, and non-viable, which includes bone and artery.

Although it might seem that any hospital would have an enormous supply of cadaver donors, retrospective evaluation has implied that only seven to ten per cent[6,8] of hospital decedents could serve as suitable kidney donors, when the cause and time of death, age and conditions of death are considered.

Logistics and Legality

Of importance also are the aspects of logistics and legality of the tissue donation. It is in the procurement of critical tissues that logistic, moral, and legal problem can seriously influence the final outcome of the attempted transplantation. For here, every second is vitally important in increasing the chances for success. Difficulty surrounds the ability to remove the organ(s) from the cadaver donor before these tissues suffer the sequel of entering in a non-living environment (hypotension, hypoxia, released intracellular enzymes from other damaged cells). This means that the closer to the exact minute of "death" the donated tissues are removed, the better are the chances that they will live when placed in the body of the recipient. Today, with our automatic respirators, external cardiac pacemakers and ventricular bypasses and assist devices, it is technically impossible for a patient to die by the previously accepted criteria of heartbeat and respiration. Thus, for transplantation to serve society for maximum benefit, some expansion of our thinking in regard to the concept of death is needed.

Criteria for Death

There is no clear agreement among transplant surgeons for the criteria which indicate death. Some imply that the electrocardiograph is of great importance. Some refer to an inactive electroencephalograph as being reliable. Others leave the fixation of time of death to the physician who cares for the donor, being careful to never have the transplant team involved with the donor until after "death" has transpired. Any criterion for death that rests on a single measurement is bound to lose many otherwise good organs while the measurements are being made. These results are always dependent upon the measurement device, the personnel using the device and other extraneous factors. The electroencephalograph, for instance is cumbersome, requires trained personnel, and is not always available. The results are not completely reliable since hypoxia (a situation that adversely affects most critical tissues) and barbiturates can give a flat tracing that later may revert to normal.[9] The electroretinal response to photic stimulation may also be a reliable index of central irreversible neuronal damage, but the difficulty in performing the test is a disadvantage.[9]

Physiologic Measurements

Another problem inherent in physiologic measurements is to define a uniform period of measurement. An occasional qrs complex is often seen on the electrocardiograph 15 minutes after "death" has occurred by all other criteria. A flat electroencephalogram is virtually impossible to obtain in even the most severely damaged neurosurgical patient because the existence of "life" and muscular movement in the body are being measured. This and the changing electrical environment nearby where various motors and appliances are being switched on and off, could generate some artificial electrical activity if hours of flatness were to be necessary. Thus, in attempting to ascertain the precise minute of "death," we cannot rely on any one vital sign or set of measurements, but must consider many such observations.

This multiplicity of factors is recognized by both the law and the medical dictionaries[10,11] when they define death as being the "apparent extinction of life as manifest by absence of heartbeat and respiration" and "the cessation of life; to cease to exist; defined by physicians as a total stoppage of the circulation of the blood, and a cessation of the animal and vital functions consequent thereon, such as respiration, pulsations, etc."

Physician Must Declare Death

In the final analysis, it is the opinion of the physician that determines the time of death regardless of what instruments or methods he uses to assess the condition. Obviously, the patient who "died" while on cardiopulmonary bypass will always have a "pulsation" (from the roller pump) and respiration (from the oxygenator initially and anaerobic cellular respiration for some time thereafter) until someone decides that the patient will not revive. Then the machines are turned off and the patient is allowed to "die" even though death has already taken place long before. Thus it should be that when, in the opinion of physicians, recovery is impossible, the organs and tissues contained in the bodies of patients suffering irreversible brain damage, unsuccessful heart surgery, or other terminal situations should be available for transplant.

"Death" should be declared when it is obvious, in the opinion of the attending (and perhaps one other) physician that recovery of an acceptable degree of the central nervous system necessary for vital function is impossible, or when the patient's disease has progressed to the point that death is inevitable within a predictably short time. Then organ preservation and/or transplantation procedures should be implemented. The responsibility of predicting that death is soon to come must remain in the hands of the attending physicians, who then contact the transplant team to take over the management of the "cadaver." This is the point in space time where death must be considered to occur. The relatives and the previously attending physicians can be comforted by the concept that although the patient died, perhaps this patient's kidneys, lung, heart, valves, or other organs will live on, and in so doing, enable some other patient to enjoy life for several more years. It is the attending physician who should inform the relatives of the patient's demise, and the transplant team should discuss tissue donation with the next of kin only after the attending physician has given permission.

Disposition of Body

The techniques and knowledge are now available to "save" more than half of the younger people (age 55 is usually chosen as an arbitrary upper limit) afflicted with kidney damage. Moreover, each year new advances are being made to improve our methods and permit the transplantation of other organs and tissues. Society must make similar advances in our laws to permit the optimum use of organs for transplantation. It is unjust to allow a person's kidneys, for instance, to die just because they reside in a host whose heart or brain is severely damaged. It is even more unjust when the recipient who could harbor these kidneys may also be condemned to die if he does not receive them.

Society already considers the needs of the majority more important than the wishes of the deceased or his family to maintain a corpse intact. This is evidenced by the fact that all states have laws by which public officials can order that autopsies be performed in certain cases, e.g., where the person died as a result of an accident or is suspected to be the victim of foul play.

In the recent medical literature,[6,13,14] reference is made to the origins of American law in the roots of early common law of England wherein a corpse did not constitute property and no property rights were associated therewith. It was assumed that the next of kin had an inherent obligation to dispose of a body and a right to direct such disposal in a dignified and acceptable fashion. It should be pointed out, however, that if the next of kin failed to uphold that responsibility, provisions were made for prompt disposal of the remains. Thus the needs of society were met by the orderly disposition of the body.

Autopsy

The laws concerning the study of the bodies of dead persons vary from state to state (Table 1). These laws can be divided into three broad categories, which are autopsy or dissection, bequest or donation for anatomical study, and disposition of unclaimed bodies.

Autopsies, or post-mortem examinations, are limited to the purpose of determining the cause of death. These can be of two types. First is the case where a coroner or other public official has jurisdiction over the body because of death occurring under unusual or suspicious circumstances, e.g., to ascertain whether death occurred as a result of criminal activity. Second are the cases in which an autopsy is sought for medical purposes. An autopsy is generally performed within a few hours after death and the body released for burial shortly thereafter.

All states need enlightened revision of their autopsy, donation, and unclaimed bodies law to catch up with the expanded transplantation technology.

Today 39 of the states have specific statutory provisions governing the performance of post-mortem examinations. Although there is considerable variety of detail in these statutes, some provisions are fairly standard.

In 17 of the states, consent for performance of the autopsy must be written regardless of who gives the consent. In five more states, written consent is not required if relatives or kin consent; but it is, if consent is given by the decedent himself.

In 20 of the 39 states having autopsy statutes, the decedent may authorize an autopsy upon his own remains. In all 39 states, consent may otherwise be obtained from kin or relatives. However, from just whom consent should be sought is often subject to a great deal of doubt. One general group of statutes does provide an order of persons based on degree of familial relationship from whom consent should be sought. Many others, however, only list those from whom consent may be obtained, but do not provide any priorities among those listed. They also usually provide that consent should

AUTOPSY AND TISSUE DONATION LAWS OF FIFTY STATES

	DONATIONS				
State	Specific Statutes	Written Form Required	Transplant Specifically Mentioned	Age of Consent	Permission Needed From:
Alabama	Yes[23]	Yes	Yes	21	Patient
Alaska	Yes[24]	Yes	Eyes only		Patient
Arizona	Yes[26]	Yes	Yes		Patient
Arkansas	Yes[28]	Yes	Yes	21	Patient
California	Yes[30]	Yes	Yes	18	Pt. or kin
Colorado	Yes[32]	Yes	Implied	13	Patient
Connecticut	Yes[34]	Yes	Yes	21	Patient
Delaware	No				
D. C.	Yes[36]	Yes	Yes	Legal	Pt. or kin
Florida	Yes[38]	Yes	Yes		Patient
Georgia	Yes[40]	Yes	Eyes Only	Legal	Patient
Hawaii	No				
Idaho	No				
Illinois	Yes[44]	Yes	Yes	(Testamentary)	Patient
Indiana	Yes[46]	Yes	Yes		Patient
Iowa	Yes[48]	Yes	Yes	21	Patient
Kansas	No				
Kentucky	Yes[50]	Yes	Yes	21	Pt. or kin
Louisiana	Yes[51]	Yes	Yes	21	Pt. or kin
Maine	Yes[52]	No	Eye & An. Sc.	21	Patient
Maryland	Yes[54]	Yes	Yes	21	Patient
Massachusetts	No				
Michigan	Yes[56]	Yes	No (Med. ed.)	Full	Patient
Minnesota	Yes[58]	Yes	No	21	Patient
Mississippi	Yes[60]	Yes	Yes	21	Patient
Missouri	Yes[62]	Yes	Yes	18	Patient
Montana	Yes[64]	Yes	Yes	18	Patient
Nebraska	Yes[66]	Yes	Yes	Will	Patient
Nevada	Yes[68]	Yes	Yes		Pt. or kin
New Hampshire	No				
New Jersey	Yes[70]	Yes	Yes		Pt. or kin
New Mexico	Yes[72]	Yes	Yes	Legal	Pt. or kin
New York	Yes[73]	Yes	Yes	18	Pt. or kin
N. Carolina	Yes[75]	Yes	Yes	Will	Pt. or kin
N. Dakota	Yes[77]	Yes	Yes	18 or with parent	Pt. or kin
Ohio	No				
Oklahoma	Yes[79]	Yes	Yes	Legal	Patient
Oregon	Yes[81]	Yes	No	(Testamentary)	Patient
Pennsylvania	Yes[83]	Yes No witness	Yes		Patient
Rhode Island	Yes[84]	Yes	Yes	Legal	Pt. or kin
S. Carolina	Yes[85]	Yes	Yes	Full	Patient
S. Dakota	Yes[87]	No	No		Pt. or kin
Tennessee	Yes[89]	Yes	No	21	Pt. or kin
Texas	Yes[91]	Yes	Yes	Legal	Patient
Utah					
Vermont	No				
Virginia	Yes[93]	Yes, will	No	21	Patient
Washington	Yes[95]	Yes	Yes	21	Pt. or kin
W. Virginia	Yes[97]	Yes	Eyes only	21	Pt. or kin
Wisconsin	Yes[99]	Yes	Yes	21	Patient
Wyoming	No	Dissection other than cause of death is felony			
Puerto Rico	Yes[102]	Yes, will	No	Will	Patient

These figures are current as of June, 1968.
Several states have additional legislation pending.

AUTOPSY AND TISSUE DONATION LAWS OF FIFTY STATES

	AUTOPSY			
State	Non-Liability Clause	Specific Statutes	Written Form Required	Permission Needed From:
Alabama	No	No		
Alaska	No	No		
Arizona	Yes	Yes[25]	No	Relative
Arkansas	Yes	Yes[27]	Yes	Pt. or kin
California	Yes	Yes[29]	Yes	Pt. or kin
Colorado	Yes	Yes[31]	No	Relative
Connecticut	No	Yes[33]	Yes	Relative
Delaware	No	No		
D. C.	No	[35]		
Florida	Yes	Yes[37]	Yes	Relative
Georgia	Yes	Yes[39]	No	Relative
Hawaii	No	Yes[41]	Yes	Relative
Idaho	No	Yes[42]	No	Relative
Illinois	Yes	Yes[43]	Yes	Pt. or kin
Indiana	Yes	Yes[45]	Yes	Relative
Iowa	No	Yes[47]	Yes	Pt. or kin
Kansas	No	Yes[106]	No	
Kentucky	No	Yes[49]	Yes	Pt. or kin
Louisiana	Yes	No		
Maine	Yes	No		
Maryland	Yes	Yes[53]	Yes	Pt. or kin
Massachusetts	No			
Michigan	Yes	Yes[55]	Yes	Kin
Minnesota	No	Yes[57]	No, except decedent	Pt. or kin
Mississippi	No	Yes[59]	No	Pt. or kin
Missouri	Yes	Yes[61]	No, except decedent	Pt. or kin
Montana	Yes	Yes[63]	No, except decedent	Pt. or kin
Nebraska	Yes	Yes[65]	Yes	Pt. or kin
Nevada	Yes	Yes[67]	No, except decedent	Pt. or kin
New Hampshire	No	No		
New Jersey	Yes	Yes[69]	Yes	Relative
New Mexico		Yes[71]	No, except decedent	Pt. or kin
New York	Yes	Yes[73]	Yes	Kin
N. Carolina	No	Yes[74]	No	Pt. or kin
N. Dakota	Yes	Yes[76]	No	Pt. or kin
Ohio	No	No		
Oklahoma	Yes	Yes[78]	No	Kin
Oregon	Yes	Yes[80]	No	Pt. or kin
Pennsylvania	No	Yes[82]	Yes	Kin or Pt. and kin
Rhode Island	No			
S. Carolina	No	Yes[107]	Yes	Pt. or kin
S. Dakota	Yes	Yes[86]	Yes	Pt. or kin
Tennessee	Yes	Yes[88]	No	Kin
Texas	Yes	Yes[90]	No	Kin
Utah	No	Yes[92]	No	Pt. or kin
Vermont	No	No		
Virginia	No			
Washington	Yes	Yes[94]	No	Pt. or kin
W. Virginia	No	Yes[96]	Yes	Kin
Wisconsin	Yes	Yes[98]	No	Kin
Wyoming	No	Yes[100]	No	Kin
Puerto Rico	No	Yes[101]	No	Relatives
	TOTALS:	39 of 50 Yes	17 Yes plus 5 if decedent	20 decedent may himself

These figures are current as of June, 1968.
Several states have additional legislation pending.

be sought from the person who has assumed custody for the purpose of burial.

Donation for Anatomical Study

A bequest or donation for anatomical study is for two general purposes: first, to make tissue available for transplantation; second, to facilitate, indeed make possible, anatomical study of the human body by medical students, etc. In this instance the body may be kept for up to a year before final disposition of the remains is made.

Because it is entirely possible for persons to die without friends or relatives to see to the disposition of their body and, because some disposition must be made, most states have laws requiring certain public officials to dispose of such bodies. A waiting period is usually required before the body is made available for anatomical study.

One of the most common provisions is that if consent is being sought from a group or class of persons in the same order of priority, consent from one shall be sufficient authorization.

In spite of the fact that eleven states have no statutes relating to autopsy and that the law in many states is unclear, it is still possible to perform autopsies with little risk of liability if certain procedures or precautions are followed. States in which no statute prescribes who has custody of a body upon death have, as part of their common law, rules determining who has custody. This is almost always, first of all, the surviving spouse. Then children, parents, and other kin in that order. Since the person with right to custody is usually the only one who can maintain an action for mutilation of the body or willful interference with the right to custody, obtaining that person's consent, preferably in writing, stops him from bringing the action. Thus the important thing to determine in non-statutory situations is: who has right to custody of the body upon death?

Although many states have no statutory provision for conduction of autopsies, nearly all have cases which set precedence in determining responsibility along family lines for the custody of the body; therein lies an implied authority to grant permission or give consent to the autopsy.

Today 40 of the states have statutes whereby a person may will or otherwise donate his body or parts thereof for various medical purposes, including transplantations.

The laws of Tennessee, Mississippi, and New Jersey clearly state that a person may dispose of his body as he sees fit, and further provide that the recipient's right to possession of the body is superior to that of the surviving spouse or next of kin, and that the gift shall not be invalid if made by will, even if the will is not offered for or admitted to probate at a subsequent date.[15]

In some states, if the whole body is donated, the donee cannot claim the body until relatives have had an opportunity to provide funeral services. It is obvious that in such a situation no critical tissues could be transplanted unless organs could be removed prior to the funeral service. However, the law is unclear as to whether tissue can be removed prior to the funeral services.

All statutes which provide for donation permit donation by the decedent himself. The instrument of donation must always be in writing, and generally must be a will, with all that a will implies with respect to validity of the donation. However, some statutes provide for deeds of gift or other written authorization, and some provide that in case the will is not offered for probate or is invalid the donation of any or all of a body is still valid. Such a non-liability provision would seem to be a necessity, because if it were necessary to wait until the will was probated, the body would be of little use for study and of no value for transplantation.

In some states the statute specifically permits relatives to make the donation. Such a provision makes the law clear; but, because only the person who has the right to custody can bring an action for mutilation of the body, it is generally possible to procure tissue in the absence of statutory authorization by obtaining this person's consent.

Although most donation statutes do not specifically name eligible donees, such a listing in a statute would appear desirable to make it clear just who is authorized to study or transplant organs from the body of the deceased.

MINNESOTA

The donation of tissues, after death of the donor, is permitted in the Bequest section of the Minnesota Statutes under the definition of wills,[16] wherein it states:

> EXECUTION OF WILL. Subdivision I. Every person of sound mind, not a minor, may dispose of his estate, or any part thereof, or any right or interest therein, by his last will in writing, signed by him or by some person in his presence and by his express direction, and attested and subscribed in his presence by two or more competent witnesses.
>
> Subdivision 2. In addition, every such person described in subdivision I may by will dispose of the whole or any part of his body to a teaching institution, university, college, state board of public health, or legally licensed hospital, either for use as such institution, university, college or hospital may see fit, or for use as expressly designated therein (1935 c 72 s 34; 1949 c 160 sl) (8992-34).

In the autopsy section,[17] dissection of "dead" human bodies is permitted as follows:

> Dead bodies; dissection; when permitted. The right to dissect the dead human being shall be limited to:
>
> a) cases specifically provided by statute, or by the direction or will of the deceased;
>
> b) cases where a coroner is authorized to hold an inquest upon the body, and then only so far as he may authorize dissection;
>
> c) cases where the husband, wife, or next of kin, charged by law with the duty of burial, shall authorize dissection for the purpose of ascertaining the cause of death, and then only to the extent so authorized, provided no dissection shall be performed pursuant to this clause if there is any objection by anyone of such next of kin.
>
> Every person who shall make, cause to procure to be made, any dissection of the body of a human being, except as herein before provided, shall be guilty of a gross misdemeanor (R.L. s 4978) (10228).

Thus dissection and presumably donation of bodies or tissues is permitted providing that either the donor's will so stated and was witnessed by two competents, or a next of kin gives his permission, and no other next of kin objects. If any of these cases were to come to court, it might become apparent that the only authorization for tissue donation would have to be based upon an ante mortum will since the definition of a will in subdivision 2 as cited above speaks only of a body, and does not label it a dead body. This distinction becomes important when we attempt to define dead body in the legal terms of the Minnesota Statutes. Under definitions of vital statistics,[20] a dead body means a lifeless human body or such parts of the human body or the bones thereof from the state of which it reasonably may be concluded that death recently occurred. Obviously, lifeless means without life, and if a body is without life, no cell therein can be alive, and therefore, the only tissues that could be so harvested would be the non-viable and non-critical tissues by this definition.

Unclaimed Bodies

In regard to unclaimed bodies, it is interesting to note that all states except Idaho have statutory provision for the disposition of unclaimed bodies without a will or known desire to the contrary, the unclaimed body becomes the property of the states to be used for the advancement of medical science. This would appear to be a good source for cadaver tissues, but it is limited at present to non-critical tissues, since all states except Idaho and Hawaii require that the body be held for a given period of time from 24 hours to several months prior to being delivered to the designated medical authorities. During this holding period, efforts must be made to locate any relatives or friends that might be interested in the body.

Persons who die in Minnesota with no relatives or friends to claim their bodies cannot, at present, be considered as a source of critical transplantable tissues because of a 36-hour waiting period required before they can be made available. This is pointed out in the "Anatomical Study" section:[18]

> DELIVERY OF SUBJECT FOR DISSECTION
>
> Except as otherwise provided in section 145.15, the bodies of all persons dying within the state and not claimed for burial within 36 hours after death shall be delivered by the person in charge thereof for purposes of anatomical study. The deans of the medical college of the state shall appoint a committee to receive such bodies, which committee shall apportion the same to the several colleges according to the numbers of their students. Any body so received shall be surrendered on demand of a relative entitled to its possession. The remains of any such body, after it has answered the purpose, shall be decently buried in a public cemetery and the expense of transporting and burying such body shall be borne by the college receiving the same (R.L. s 2152) (5392).
>
> WHAT BODIES EXCEPTED
>
> No body shall be so delivered
>
> (1) After it has been regularly interred.
>
> (2) After it has been claimed for burial or cremation, by any person entitled to receive it for such purpose.
>
> (3) Without the consent of all known relatives of the person deceased.

(4) If such person in his last sickness requested that his remains be burned.
(5) If he died while detained as a witness or under suspicion of crime, or
(6) If by any provision of the law another disposition thereof be required (R.L. s 2153) (53 3).

If "purposes of anatomical study" were to be interpreted as including transplantation, penalties are provided for anyone using these "unclaimed" bodies for transplantation tissues inasmuch as[19] it is provided that:

> Every person who shall fail to comply with the provisions of sections 145.15 (what bodies excepted) and 145.16 (delivery of bodies) shall be guilty of a misdemeanor, the minimum punishment whereof shall be a fine of $25. Every person who shall use any body mentioned in sections 145.15 and 145.16 for a purpose other than that contemplated therein, or who shall remove it from the state, or in any manner traffic therein, or refuse to deliver the same upon proper demand, shall be guilty of a gross misdemeanor.

Comments

In comparison to the rest of the country, Minnesota is well ahead of the least progressive states, but somewhat behind the more forward-thinking regions. The time is ripe for change. A uniform gift-of-human-tissues act has been drafted which incorporates the best aspect of present laws,[105] recent advances in transplantation have demonstrated the need for a law which goes beyond the confines of present legal concepts. Since transplantation is now a well-established practice and a field that is receiving enormous amounts of federal funds to help its growth, and since Minnesota has its share of physicians interested in transplantation, it behooves us to alter our laws to bestow the most good upon the most people, while considering the individual rights of both donor and donee: that is, to encourage the donation of organs in numbers as great as possible, and still protect the rights of the donating individual and the sensitiveness of his relatives. In the prior act asking the next of kin of a soon-to-die donor for his tissue was a monumental and morbid task. Surprisingly many people even in that hour of grief, were able to permit the donation. To discuss the prospect of donation with a possible donor after his death has become predictable, but before he was moribund, is almost unthinkable from a psychological standpoint. This burden should be lifted from the patients and from the transplant team.

The need to move as quickly as possible, in order that the critical tissues for transplantation may have the best possible chance, militates against the filling out of forms with witnesses, signatures, statements of limitation, etc. At present, all this must be done before the anticipated transplant time.

The earlier a donation source can be predicted, the greater is the opportunity to begin tissue compatibility tests and assure the greatest possible chance for a successful transplant. Thus, potential donors might be partially evaluated long before they become moribund . . . if every patient could be considered a potential donor.

The legislation that is needed to allow the maximum number of lives to be saved by transplantation must establish that when we die, we have no further use for our bodies. This is evidenced by the rapid way they decay if not carefully preserved. Since the living population has a great stake in keeping all its members alive and healthy, and since the needs of the living take precedence over consideration for the dead as the Supreme Court of Nebraska pointed out in a 1964 case:[102]

> The right to have a dead body remain unmolested is not an absolute one; it must yield where it conflicts with the public good or where the demands of justice require subordination (Stastny vs. Tachovsky, 132 NW 2 d 317).

Therefore, it must be resolved that all efforts be made to keep organs and tissues alive and functioning. In an effort to do so, the law needs revision to allow donation of tissue automatically. If, for some religious or other reason, anyone objects to helping another human being live with a gift of his organs, the wishes of the individual donor should prevail. And, if the next of kin of a terminal patient should feel that their relative's tissues should be destroyed by cremation or burial immediately upon death, instead of living on in the body of some desperate child for 40 or 60 more years, their wishes too should be respected. When these changes in law come about, the last-minute legal aspects (which may have been useless at best, and fraudulent at worst) will be avoided. By assuming that saving a life is more valuable to society than destroying a whole body with all its parts, we place the burden of responsibility for initiating burial and the resultant destruction on those who want the tissues to be buried. The law could be written, however, in such a way as to avoid any mutilation or change in appearance and to maintain the present funeral practices.

Legislation designed to enhance the extension of life through transplantation techniques is greatly needed because of problems associated with transplantation not present under earlier medical practices. First is the need for large quantities of tissues, which are practically impossible to salvage under present legal procedures. Second is that speed is of the utmost importance in the procurement of tissues. The decision to transplant must be made before or very shortly after death; present legal procedures do not as a practical matter permit this to be done. The proposed legislation is an attempt to meet both of these needs and yet to preserve the basic rights of everyone involved.

Although much time and effort was expended by the authors to construct new legislation to accomplish all these aims, the *Uniform Anatomical Gift Act* developed by the National Conference of Commissioners on Uniform State Laws is now considered adequate on each of these points. In addition, it carries the approval of the National Conference, the National Research Council, The American Bar Association, and four states have recently enacted laws based on earlier drafts of the Uniform Act. We, therefore, suggest that the Uniform Anatomical Gift Act be enacted with all due haste, and in the form presented.

UNIFORM ANATOMICAL GIFT ACT

(Copy of final draft as approved on July 30, 1968, by the National Conference of Commissioners on Uniform State Laws)

An act authorizing the gift of all or part of a human body after death for specified purposes.

Section 1. (Definitions)

(a) "Bank or storage facility" means a facility licensed, accredited or approved under the laws of any state for storage of human bodies or parts thereof.

(b) "Decedent" means a deceased individual and includes a stillborn infant or fetus.

(c) "Donor" means an individual who makes a gift of all or part of his body.

(d) "Hospital" means a hospital licensed, accredited or approved under the laws of any state and includes a hospital operated by the United States government, a state or a subdivision thereof, although not required to be licensed under state laws.

(e) "Part" includes organs, tissues, eyes, bones, arteries, blood, other fluids and other portions of a human body, and "part" includes "parts."

(f) "Person" means an individual, corporation, government or governmental subdivision or agency, business trust, estate, trust, partnership or association or any other legal entity.

(g) "Physician" or "surgeon" means a physician or surgeon licensed or authorized to practice under the laws of any state.

(h) "State" includes any state, district, commonwealth, territory, insular possession, and any other area subject to the legislative authority of the United States of America.

Section 2. (Persons Who May Execute an Anatomical Gift)

(a) Any individual of sound mind and 18 years of age or more may give all or any part of his body for any purposes specified in section 3, the gift to take effect upon death.

(b) Any of the following persons, in order of priority stated, when persons in prior classes are not available at the time of death, and in the absence of actual notice of contrary indications by the decedent, or actual notice of opposition by a member of the same or a prior class, may give all or any part of the decedent's body for any purposes specified in Section 3.

(1) the spouse,
(2) an adult son or daughter,
(3) either parent,
(4) an adult brother or sister,
(5) a guardian of the person of the decedent at the time of his death.
(6) any other person authorized or under obligation to dispose of the body.

(c) If the donee has actual notice of contrary indications by the decedent, or that a gift by a member of a class is opposed by a member of the same or a prior class, the donee shall not accept the gift. The persons authorized by subsection (b) may make the gift after death or immediately before death.

(d) A gift of all or part of a body authorizes any examination necessary to assure medical acceptability of the gift for the purposes intended.

(e) The rights of the donee created by the gift are paramount to the rights of others except as provided by section 7(d).

Section 3. (Persons Who May Become Donees, and Purposes for Which Anatomical Gifts May Be Made)

The following persons may become donees of gifts of bodies or parts thereof for the purposes stated:

(1) Any hospital, surgeon, or physician, for medical or dental education, research, advancement of medical or dental science, therapy or transplantation; or

(2) any accredited medical or dental school, college or university for education, research, advancement of medical or dental science or therapy; or

(3) any bank or storage facility for medical or dental education, research, advancement of medical or dental science, therapy or transplantation; or

(4) any specified individual for therapy or transplantation needed by him.

Section 4. (Manner of Executing Anatomical Gifts)

(a) A gift of all or part of the body under section 2 (a) may be made by will. The gift becomes effective upon the death of the testator without waiting for probate. If the will is not probated, or if it is declared invalid for testamentary purposes, the gift, to the extent that it has been acted upon in good faith, is nevertheless valid and effective.

(b) A gift of all or part of the body under section 2 (a) may also be made by document other than a will. The gift becomes effective upon the death of the donor. The document, which may be a card designed to be carried on the person, must be signed by the donor, in the presence of 2 witnesses who must sign the document in his presence. If the donor cannot sign, the document may be signed for him at his direction and in his presence, and in the presence of 2 witnesses who must sign the document in his presence. Delivery of the document of gift during the donor's lifetime is not necessary to make the gift valid.

(c) The gift may be made to a specified donee or without specifying a donee. If the latter, the gift may be accepted by the attending physician as donee upon or following death. If the gift is made to a specified donee who is not available at the time and place of death, the attending physician upon or following death, in the absence of any expressed indication that the donor desired otherwise, may accept the gift as donee. The physician who becomes a donee under this subsection shall not participate in the procedures for removing or transplanting a part.

(d) Notwithstanding section 7(b), the donor may designate in his will, card or other document of gift the surgeon or physician to carry out the appropriate procedures. In the absence of a designation, or if the designee is not available, the donee or other person authorized to accept the gift may employ or authorize any surgeon or physician for the purpose.

(e) Any gift by a person designated in section 2(b) shall be made by a document signed by him, or made by his telegraphic, recorded telephonic or other recorded message.

Section 5. (Delivery of Document of Gift)

If the gift is made by the donor to a specified donee, the will, card, or other document, or an executed copy thereof, may be delivered to the donee to expedite the appropriate procedures immediately after death, but delivery is not necessary to the validity of the gift. The will, card or other document, or an executed copy thereof, may be deposited in any hospital, bank or storage facility or registry office that accepts them for safekeeping or for facilitation of procedures after death. On request of any interested party upon or after the donor's death, the person in possession shall produce the document for examination.

Section 6. (Amendment or Revocation of the Gift)

(a) If the will, card or other document or executed copy thereof has been delivered to a specified donee, the donor may amend or revoke the gift by:

(1) the execution and delivery to the donee of a signed statement, or

(2) an oral statement made in the presence of 2 persons and communicated to the donee, or

(3) a statement during a terminal illness

or injury addressed to an attending physician and communicated to the donee, or

(4) a signed card or document found on his person or in his effects

(b) Any document of gift which has not been delivered to the donee may be revoked by the donor in the manner set out in subsection (a) or by destruction, cancellation, or mutilation of the document and all executed copies thereof.

(c) Any gift made by a will may also be amended or revoked in the manner provided for amendment or revocation of wills, or as provided in subsection (a).

Section 7. (Rights and Duties at Death)

(a) The donee may accept or reject the gift. If the donee accepts a gift of the entire body, he may, subject to the terms of the gift, authorize embalming and the use of the body in funeral services. If the gift is of a part of the body, the donee, upon the death of the donor and prior to embalming, shall cause the part to be removed without unnecessary mutilation. After removal of the part, custody of the remainder of the body vests in the surviving spouse, next of kin or other persons under obligation to dispose of the body.

(b) The time of death shall be determined by a physician who attends the donor at his death, or, if none, the physician who certifies the death. This physician shall not participate in the procedures for removing or transplanting a part.

(c) A person who acts in good faith in accord with the terms of this Act, or under the anatomical gift laws of another state (or a foreign country) is not liable for damages in any civil action or subject to prosecution in any criminal proceeding for his act.

(d) The provisions of this Act are subject to the laws of this state prescribing powers and duties with respect to autopsies.

Section 8. (Uniformity of Interpretation)

This Act shall be so construed as to effectuate its general purpose to make uniform the law of those states which enact it.

Section 9. (Short Title)

This Act may be cited as the Uniform Anatomical Gift Act.

Robert A. Ersek, M.D.*
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From the University of Minnesota, Minneapolis, Minnesota.

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4-107. May be secured from the author or the reprints.

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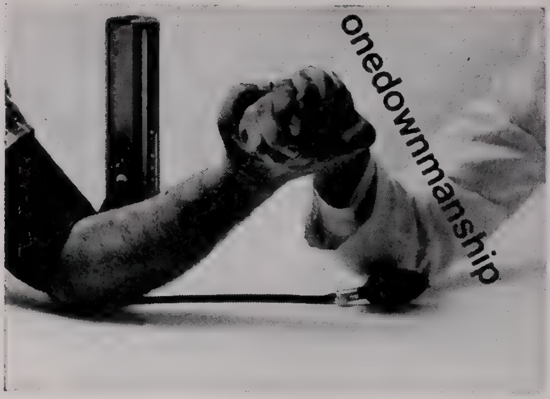

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Abstracts, Briefs and Commentaries

THE PYLORUS AS A BARRIER TO REFLUX

The gastroduodenal junction has been extensively studied in the past from the viewpoint of its relationship to gastric emptying, and its role as a pump and as a filter established. This paper deals with a clinical radiological study of the pylorus in 400 patients, assessing its efficiency as a barrier to duodenal regurgitation.

Results indicate that the normal pylorus is a competent structure preventing reflux during duodenal cap diastole and also during systolic contraction of a full cap. Such competence can easily be demonstrated in healthy nondyspeptic individuals and in many cases of duodenal ulcer. In the dyspepsias associated with gastric mucosal disease, especially gastric ulcer, there appears to be a breakdown in sphincter competence.

The sphincter is incompetent in 96% of active simple gastric ulcers, in 100% of combined duodenal and gastric ulcers, in 60% of duodenal ulcers, in 56% of patients with symptomatic hiatus hernia, and in 80% of X-ray negative dyspeptics. In biliary tract disease the sphincter behaves normally unless there is an associated dyspepsia, when incompetence is the rule.

These results add weight to the hypothesis that reflux of duodenal contents is abnormal and may play a part in human gastric pathology.

W. M. Capper, M.D., J. O. Kilby, M.D.,
G. R. Airth, M.D., M. J. Gibson, M.D.*
Bristol, England

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*Departments of Gastroenterology and Radiology, Southmead Hospital, and Departments of Radiology, Bristol Group of Hospitals, Bristol.

Abstract of presentation made during Congressus Gastroenterologiae Internationalis, VIII, in Prague, 1968.

SERUM ENZYME STUDIES IN RELATION TO THE PANCREATITIS OF PREGNANCY

It seems to be reasonably well accepted that there is an increased incidence of acute pancreatitis in pregnancy. This is a serious disease with a high mortality rate. The condition may be due to an underlying pancreatic disturbance preceding pregnancy. This is not a universal rule. Recurrence of pancreatitis in further pregnancies is not inevitable. We have studied levels of serum amylase, lipase and anti-trypsins in the sera of normal pregnant women over the months of pregnancy. The levels of these substances are elevated in the last trimester. This is not necessarily in parallel for each of the three. The levels reach a maximum about term. The mean figure reached is at the upper limit of the normal range. Absolute levels would be greater if the extra body water of pregnancy were allowed for. We have studied a limited group of patients using the serum evocative test with secretin and pancreozymin as stimulants. The response of the serum levels following pancreatic stimulation in such subjects is also at the upper limit of the normal range or may exceed it, especially in the last trimester. Somewhat analogous changes in the levels of these enzymes occur during the menstrual cycle. This may be relevant to the changes found in normal pregnancy and to the pathogenesis of pregnancy pancreatitis.

O. FitzGerald, M.D., M. Carey, M.D., K. McGeeney, M.D., J. Reynolds, M.D.*
Dublin, Ireland

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*Department of Medicine and Therapeutics, University College, Dublin.

Abstract of presentation made during Congressus Gastroenterologiae Internationalis, VIII, in Prague, 1968.

DETERMINATION OF GASTRIC SECRETION USING A STEADY STATE TECHNIQUE AS A GUIDE FOR THE ELECTIVE SURGERY FOR PEPTIC ULCER

In order to obtain a preoperative evaluation of the gastric secretion, the steady technique by Nordgren has been performed on patients with gastric or duodenal ulcer. Some 75 patients with peptic ulcer have been investigated. Patients with duodenal ulcer often have a higher volume secretion than normal individuals. The relationship between volume secretion and acidity was, however, found to be within normal limits. Patients with gastric ulcer have normal volume secretion but often a lower acidity. This was most obvious at submaximal stimulation. We are now performing more radical surgery on patients with high secretion and less radical on patients with low secretion and low acidity. In this way we intend to get a low frequency of recurrences in combination with a low rate of postgastrectomy disturbances.

S. Dahlgren, M.D., B. Nordgren, M.D.*
Uppsala, Sweden

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*Departments of Surgery and of Clinical Physiology, University Hospital, Uppsala.

Abstract of presentation made during Congressus Gastroenterologiae Internationalis, VIII, in Prague, 1968.

Minnesota Medicine Cover Photographs

In order to encourage more physicians to submit color slides for use on the cover of MINNESOTA MEDICINE the competition is being discontinued. The picture editor now invites all physician-photographers to send 35 mm. color slides of suitable subjects for consideration as cover pictures. The format must be horizontal because of printing limitations. Pictures highlighting Minnesota seasons, places, and activities will have an automatic advantage. No limit as to the number of slides sent will be set, but all slides should be individually identified. All slides will be returned. Physicians whose pictures are used as covers will be recognized in MINNESOTA MEDICINE. We can use many more pictures than we have received in the past.

Book Reviews

The books which help you most are those which make you think the most.—
Theodore Parker

MENIERE'S DISEASE MECHANISM AND MANAGEMENT, M. Spencer Harrison, M.D., F.R.C.P., F.R.C.S., and Lionel Naftalin, B.Sc., FC. Path., Pp. 226. Charles C. Thomas, Publisher.

This book is a comprehensive treatise on Meniere's disease, its possible causes and treatment. All related phases of basic research on the labyrinth, its structure, and function are discussed in accordance with current thinking.

The chapters are integrated essays on all facets pertinent to Meniere's disease. Three chapters in particular: "The Natural History of Meniere's Disease," "Difficulties in Diagnosis," and "Treatment," should be read by every physician who treats a dizzy patient.

The authors' aim . . . "to fit together the many intriguing pieces of research on the contents of the labyrinth in the past two decades," is attempted in the chapters on "Histopathology and Physiology and Biochemistry of the Labyrinthine Fluids." Various theories regarding origin of endolymph, and distention of the endolymphatic system are presented. An amazing bibliography has been compiled here, and I feel this book is worth purchasing for this reason alone.

A monograph on Meniere's disease fills a periodic need for otolaryngologists. Certainly in the past decades, with the development of ultramicrochemical techniques and the use of the electron microscope in the study of normal and also pathological specimens, a tremendous amount of new knowledge has accrued. The authors have done a good job of gathering all this information, organizing and contributing their own original work to it, and presenting it to the reader in an interesting fashion.

Hyman M. Paisner, M.D.
Minneapolis, Minnesota

ANATOMY FOR SURGEONS, Vol. 1, The Head & Neck, 2nd Edition, W. Henry Hollinshead, Ph.D.; Hoeber Medical Division, Harper & Row, New York, N. Y.; Price: $20.00; 634 pages; illustrations: 600.

This Anatomy of the Head and Neck is an excellent monograph for the surgeon in clinical practice. The details of complete descriptive anatomy are not included, but anatomical structures and variations are well described and beautifully illustrated with line drawings. This gives the clinical surgeon an opportunity to review the anatomy under consideration and have readily at hand the variations which might be encountered in the course of a surgical operation.

This will be particularly useful to the ophthalmologist and to the otolaryngologist. Chapter 9 deals with Surgery of the Neck which in most circumstances will probably be useful to the surgeon who does goiter surgery and neck dissections.

The illustrations are labeled in chapter sequence so that the first number indicates the chapter and the subsequent numbers indicate the sequence within the chapter. The headings and sub-headings are well placed and the type faces are large enough to be easily read without eye strain.

Carl O. Rice, M.D.
Minneapolis, Minnesota

CALCULATION OF INDUSTRIAL DISABILITIES OF THE EXTREMITIES AND THE BACK—Second Edition—Carl O. Rice, M.D., Ph.D., F.A.C.S.; Publisher: Charles C. Thomas, Springfield, Illinois; Pages: 170; Illustrations: 148.

While admiring very much the precise and objective system of calculation which the author has evolved, it is felt that the method is so far removed from the basic principles applied to such calculations in Switzerland that Swiss surgeons will hardly be able to use it in calculating the disabilities of their patients.

The major discrepancy between the American and the Swiss system is that apparently in the United States a disability is calculated strictly on the basis of anatomical and functional defects without regard for the profession of the patient, whereas in Switzerland a given anatomo-functional impairment is evaluated on the basis of the disability it causes the patient in his individual profession.

The author has pointed out (page 83) that the physician should take the responsibility of accurately determining physical disability of an industrial member, but the Industrial Commission should establish the remunerative award in accordance with the individual's employment.

K. Küpfer, M.D.
P. Lundsgaard-Hansen, M.D.
Berne, Switzerland

(Continued from page 182)

THE WEST MEDICAL CLINIC **has an opening** for a General Practice Physician. This is a five man group that conducts a practice near downtown St. Paul and also has the Airport Medical Clinic at Wold Chamberlain Field, Twin City International Airport. Both clinics have full laboratory and X-ray services with technologists covering both fields.

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Erratum

In the November, 1968, issue of Minnesota Medicine, Page 1618, "Coarctation of Aorta as Part of Shone Syndrome," there is an error in the stated Lanoxin dosage. In the sixth line from the top of the page, it should read 0.07 mg. Lanoxin per kilogram instead of 0.7.

George R. Noren, M.D.
Assistant Chief, Pediatrics
Hennepin County General Hospital

Meetings and Announcements

A wise man is strong; yea, a man of knowledge increaseth strength. Old Testament: Proverbs, xxiv, 5.

JANUARY

Zumbro Valley Medical Society. Regular Meeting, Mann Hall, 7 P.M., January 8.
Minnesota Academy of Medicine. Town & Country Club, St. Paul, 6 P.M., January 8.
Minnesota Academy of Ophthalmology and Otolaryngology. Regular Meeting, Minnesota Club, St. Paul, January 10, Dinner, 7 P.M., Meeting, 8 P.M.
Stearns-Benton County Medical Society. Scientific Program, St. Cloud Hospital of Nursing, 1:30 P.M., January 11. Auxiliary Program, to be announced. Evening: Dinner—Germain Hotel, St. Cloud.
Hennepin County Medical Society. Regular Meeting, Pick-Nicollet Hotel, Minneapolis, 6 P.M., January 13.
Brown County Medical Society. Annual Meeting, Tropicana, New Ulm, 7 P.M., January 14.
Winona County Medical Society. Annual Meeting, Williams Hotel, 7 P.M., January 14.
Blue Earth Valley Medical Society. Regular Meeting, Interlaken Golf Club, Fairmont, 7 P.M., January 15.
McLeod County Medical Society. Regular Meeting, Location to be announced, 6:30 P.M., January 16.
Twin City Urological Society. Town & Country Club, St. Paul, 6 P.M., January 17.
Steele County Medical Society. Inn Towne Motel, Owatonna, 6:30 P.M., January 21.
Blue Earth County Medical Society. Century Club, 7 P.M., January 27.
Range Medical Society. Annual Meeting, Hibbing, Dinner, 7:15 P.M., January 28.

FEBRUARY

Scott-Carver County Medical Society. Regular Meeting, Wagner's Supper Club, Jordan, 6:30 P.M., February 4.
Minnesota Academy of Medicine. Town & Country Club, St. Paul, 6 P.M., February 12.
Minnesota Academy of Ophthalmology & Otolaryngology. Regular Meeting, Minneapolis Athletic Club, Dinner, 7 P.M., Meeting 8 P.M., February 14.
Minnesota Radiological Society. Winter Meeting—Symposium on Coronary Arteriography, Sheraton-Ritz Hotel, Minneapolis, February 15.
Blue Earth Valley Medical Society. Regular Meeting, Interlaken Golf Club, Fairmont, 7 P.M., February 19.

Thirty-Second Annual Meeting The New Orleans Graduate Medical Assembly

The thirty-second annual meeting of The New Orleans Graduate Medical Assembly will be held March 10, 11, 12, 13, 1969, headquarters at The Roosevelt Hotel.

Nineteen outstanding guest speakers will participate and their presentations will be of interest to both specialists and general practitioners. The program will include fifty informative discussions on many topics of current medical interest, in addition to a clinicopathologic conference, medical motion pictures, round-table luncheons, and technical exhibits. This program is acceptable for three and one-half (3½) prescribed hours and twenty-eight (28) elective hours by the American Academy of General Practice.

An interesting and enjoyable program of entertainment for visiting ladies has been planned.

Electroencephalography Course

A Course in Current Problems in Electroencephalography: Advances toward their Solution; Date: March 13-15, 1969, Place: Houston, Texas. Sponsors: The American Electroencephalographic Society and Baylor University College of Medicine. For further information contact: Dr. Peter Kellaway, Baylor University College of Medicine, Texas Medical Center, Houston, Texas 77025.

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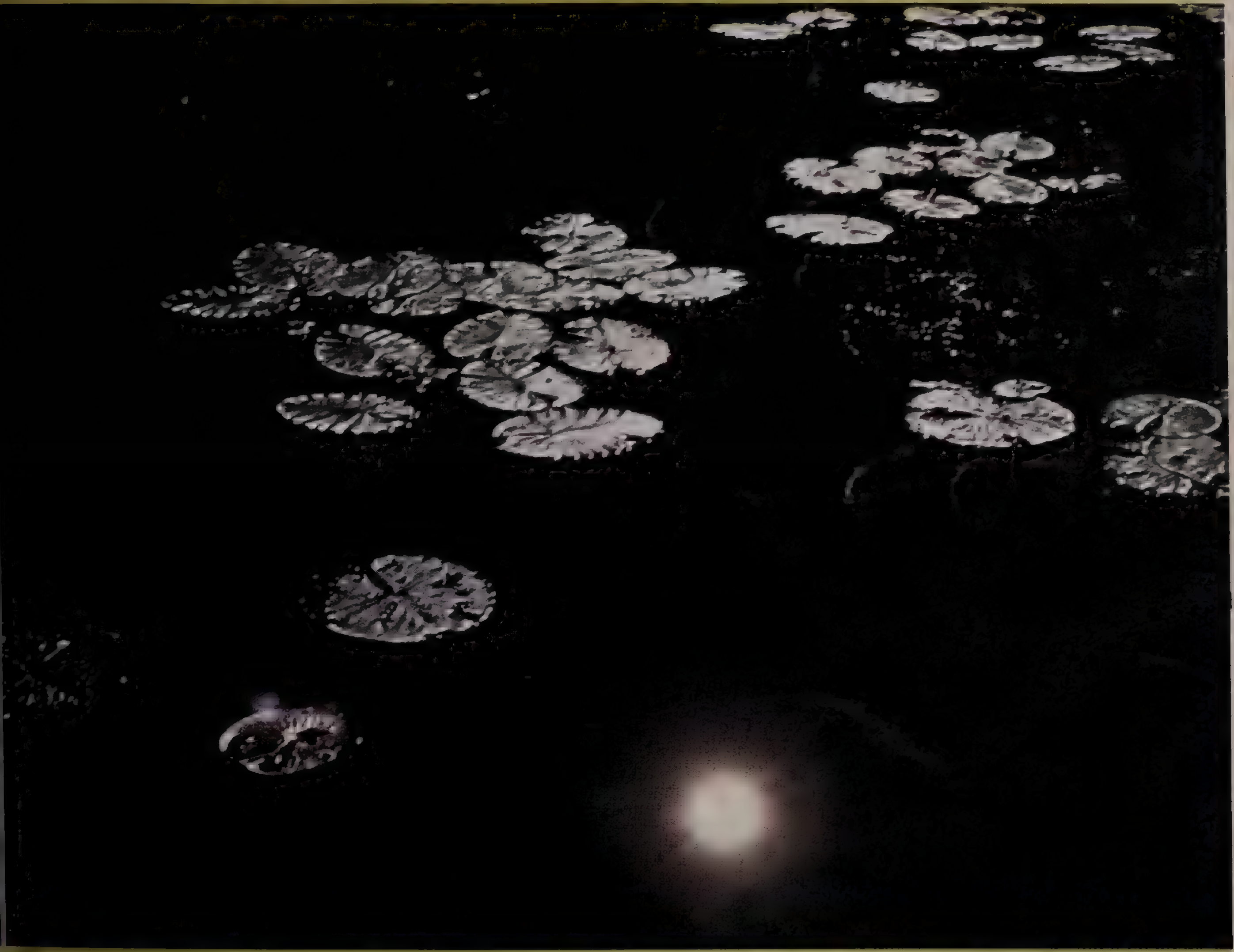

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FEBRUARY, 1969

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References: 1. Merck & Co., Merck Chemical Division: Antacid Literature Survey, Rahway, New Jersey. (MM3041, R-1286-K REV 463.) 2. Danhof, I.E., report on file. 3. Hoon, J.R.: Arch. Surg. *93*:467 (Sept.) 1966.

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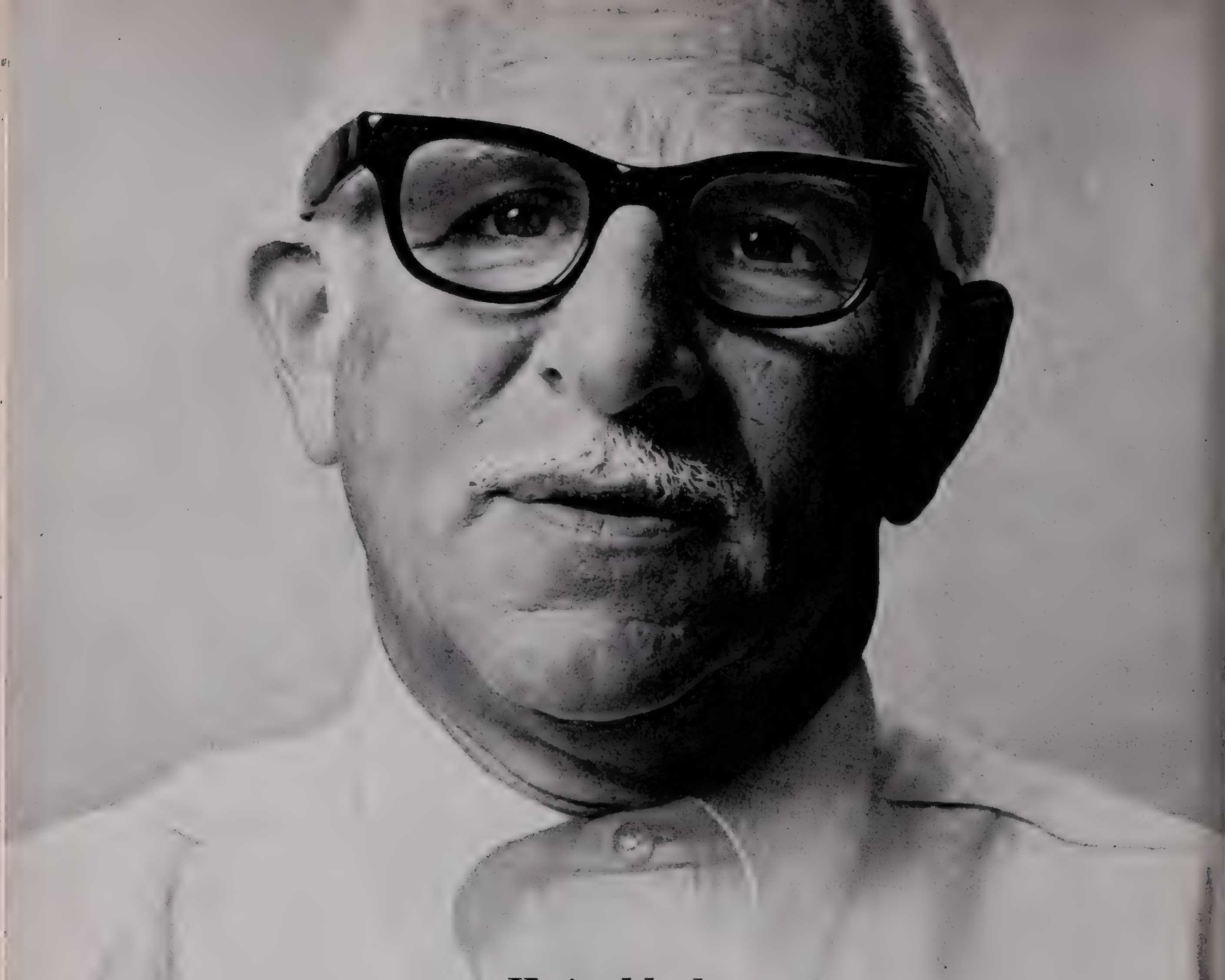

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cessation of treatment.

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rhea, stomatitis, glossitis, enterocolitis, pruritus ani. Skin—maculopa
ular and erythematous rashes; a rare case of exfoliative dermatitis h
been reported. Photosensitivity; onycholysis and discoloration of t
nails (rare). Kidney—rise in BUN, apparently dose related. Transie
increase in urinary output, sometimes accompanied by thirst (rare
Hypersensitivity reactions—urticaria, angioneurotic edema, anaphylaxi
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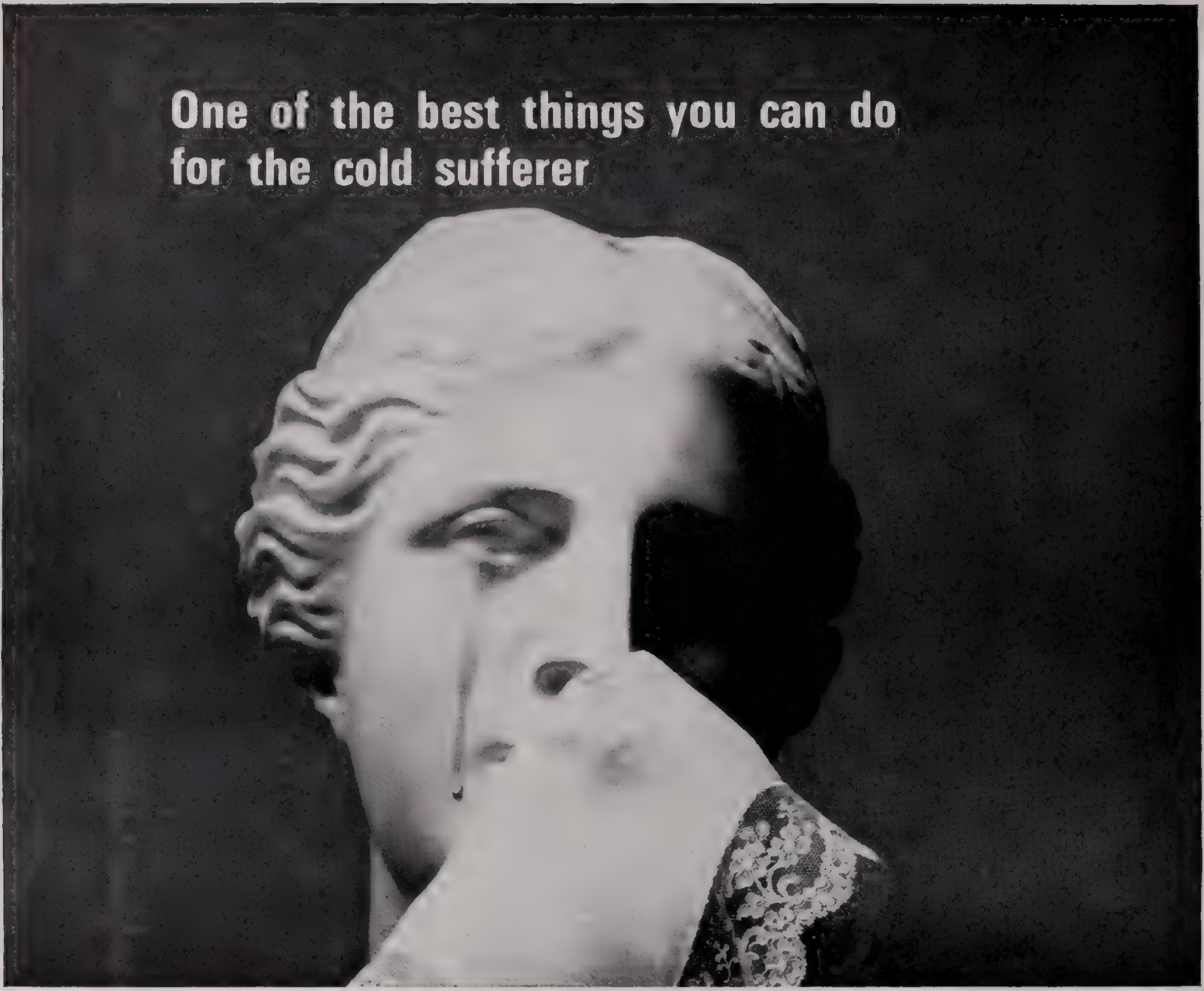
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President's Letter

Minnesota Radiological Society

On behalf of the Minnesota Radiological Society, I appreciate being invited to write this month's President's Letter. Last year marked the fortieth anniversary of the Minnesota Radiological Society. Dr. Leo G. Rigler, who for so many years was professor of radiology at the University of Minnesota, served as the first president of the society in 1928-1929; and he was followed in office by the late Dr. B. R. Kirklin of the Mayo Clinic. From a founding membership of about 20 radiologists, the society has grown to include more than 160 radiologists, physicists, and radiobiologists.

As the society has grown, so have its areas of interest. In the beginning the sharing and dissemination of scientific knowledge was the primary concern. More recently the society has become active in the area of socio-medical economics in addition to maintaining its scientific stature.

One cannot help but feel that radiology is presently in one of the most exciting eras of its existence. The past few years have seen the development of diagnostic radiologic procedures little short of phenomenal, particularly in its vascular, neurologic, and isotopic techniques. Therapeutic radiology has achieved parallel development, as evidenced by cobalt teletherapy, the linear accelerator, the betatron, and the therapeutic isotopes.

In the realm of medical economics the greatest breakthrough has been the advent of separate billing. This single mechanism has done more to make the radiologist a physician like other physicians than anything else that has happened since the inception of radiology as a specialty. Under this system the radiologist bills for the professional service he has rendered in the examination or treatment of a patient, and the hospital bills for the technical component of the examination or treatment. Thus the radiologist has a position analogous to that of other physicians such as surgeons who bill for the surgical operation while the hospital bills for the use of the operating room and equipment.

It is perhaps unfortunate that the radiologist has come to be thought of as a hospital-based physician, because actually in most cases he is not. According to a survey published in *Patterns,* a publication of Parke-Davis, radiologists spend about 19% of their work week in hospitals, which is considerably less time than is spent by many of their medical and surgical colleagues.

Like most physicians, radiologists are in short supply; and this pinch is evident in Minnesota as elsewhere. Organized radiology from the grass-roots radiologist up through the American College of Radiology is working actively to interest more young physicians in our specialty. We are also expanding the training of pararadiologic personnel. Within our ranks there is currently debate regarding just how much patient responsibility and even preliminary film interpretation should be relegated to the technologist. In my opinion the acute shortage of radiologists will soon make such debate merely academic. Undoubtedly we will find it more important to get on with the

Continued on page 271

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Precautions: Use cautiously, if at all, in a patient with a strongly positive history of allergy.

In prolonged therapy with penicillin, and particularly with high parenteral dosage schedules, frequent evaluation of the renal and hematopoietic systems is recommended.

In suspected staphylococcus infections, proper laboratory studies (including sensitivity tests) should be performed.

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The Anatomy of the Facial Nerve

GEORGE L. KULLMANN, M.D.*
D. THANE R. CODY, M.D., Ph.D.†
Rochester, Minnesota

CONTROL OF THE FACIAL nerve originates in the motor cortex of the frontal lobe of the brain. From this region the supranuclear motor fibers converge via the pyramidal tracts onto the facial nuclei in the pons (Figure 1). Most of the fibers cross to reach the seventh nucleus of the opposite side, but some fibers proceed to the ipsilateral nucleus and eventually innervate the orbicularis oculi and frontalis muscles. Thus, a unilateral supranuclear lesion, which interrupts these fibers, will produce a spastic paralysis of only the lower half of the contralateral side of the face, whereas a lower-motor-neuron lesion results in a flaccid paralysis of the entire ipsilateral half of the face.

Motor Nucleus

The motor nucleus of the seventh cranial nerve is located in the pons, in close relationship to the abducens and salivary nucleus, as well as the spinal nucleus of the trigeminal nerve and the nucleus of the tractus solitarius (Figure 2). As the motor fibers leave the facial nucleus, they course around the nucleus of the abducens nerve and thus form the "genu of the facial nerve." The fibers then emerge from the caudal end of the pons, dorsal to the sixth cranial nerve and ventral to the eighth cranial nerve.

The Nervus Intermedius

These fibers are then joined by the nervus intermedius (of Wrisberg) to form the seventh cranial nerve. The nervus intermedius carries the parasympathetic visceromotor fibers from the salivary nuclei to the submandibular, sublingual, and lacrimal glands. The fibers to the lacrimal gland travel from the seventh nerve complex in the greater petrosal nerve and to the submandibular and sublingual glands in the chorda tympani nerve. The chorda tympani

---

*Mayo Graduate School of Medicine (University of Minnesota), Rochester: Resident in Otolaryngology and Rhinology.

†Mayo Clinic and Mayo Foundation: Section of Otolaryngology and Rhinology.

Read at the meeting of the Minnesota Academy of Ophthalmology and Otolaryngology, Rochester, Minnesota, May 13, 1968.

The terminology of the Nomina Anatomica 1965, 3rd Edition, is used, with naming of the intratemporal portions of the facial nerve according to House.

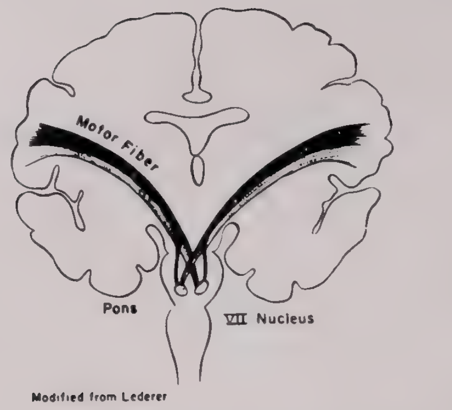

Fig. 1—Supranuclear motor fibers of facial nerves. (From: Kettel, K.: Peripheral Facial Palsy: Pathology and Surgery. Springfield, Ill., Charles C Thomas, Publisher and Copenhagen, Munksgaard, 1959, 341 pp. By permission of the publisher.)

nerve also carries special visceral afferent fibers, which supply the sensation of taste to the anterior two thirds of the tongue through the nervus intermedius and thence to the brain stem. In addition, it is believed that the nervus intermedius carries some general visceral afferents, which supply deep sensibility to the face and superficial tactile sensation to the posterior wall of the external auditory meatus.

Cerebellopontine Angle

This first part of the facial nerve is called the "cerebellopontine angle portion," and on its way to the internal acoustic meatus, it lies on the concave upper surface of the eighth cranial nerve. It enters the facial (fallopian) canal of the petrous portion of the temporal bone at the fundus of the internal acoustic meatus and is separated from the cochlear and inferior vestibular nerves by a transverse (falciform*) crest of bone and from the superior vestibular nerve by a vertical crest of bone (Figure 3). As the nerve enters the fallopian canal, it becomes the labyrinthine portion. This segment of the facial nerve takes a slightly curving course, the concavity of the flexure being an accommodation to the basal turn of the cochlea, to reach the geniculum.

The Geniculum

At this point, located in the medial wall of the epitympanic recess, the nerve turns suddenly posteriorly above the promontory. This sharp bend in the nerve is called the geniculum and is the area where the geniculate ganglion is located. Also here the greater petrosal nerve is given off, as well as a small branch to the lesser petrosal nerve. A third nerve may also branch off here, the external petrosal, which is an inconstant branch from the geniculate ganglion to the sympathetic plexus of the middle meningeal artery.

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*See Test Your Word Score Page 265.

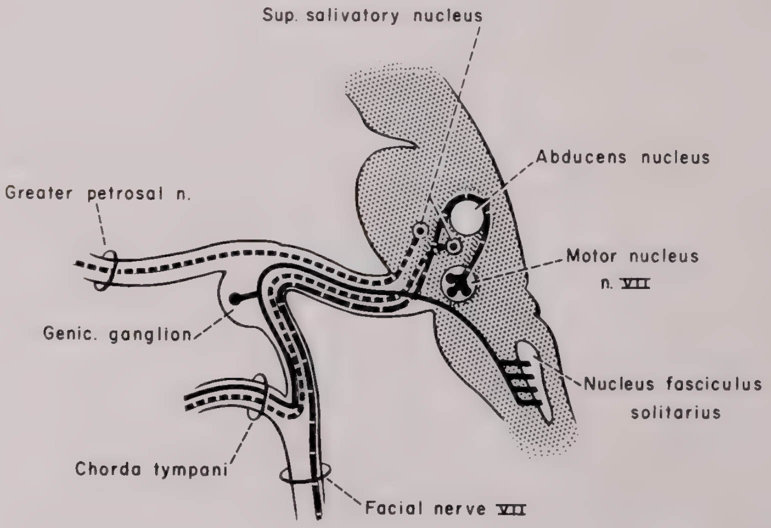

Fig. 2—Nuclear relationships of facial motor and sensory fibers.

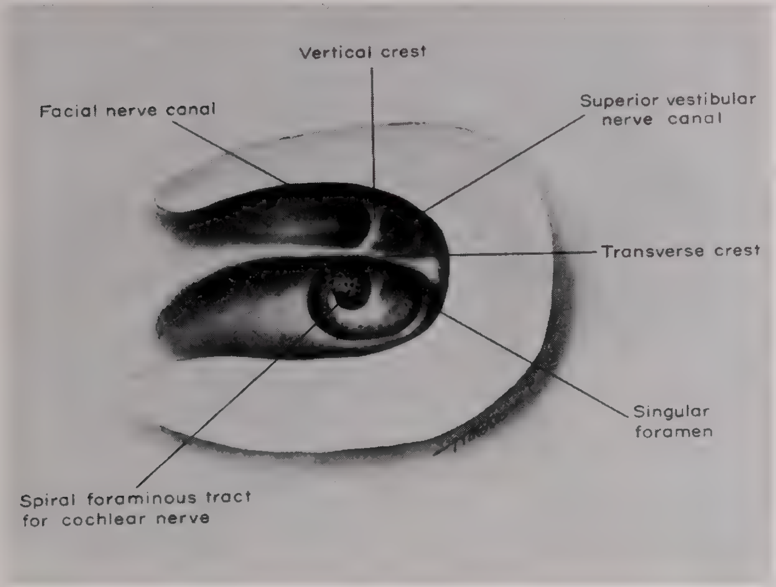
Vertical crest
Facial nerve canal
Superior vestibular nerve canal
Transverse crest
Singular foramen
Spiral foraminous tract for cochlear nerve

Fig. 3—Diagram of right internal acoustic meatus, level of fundus. (From Pulec, J. L.: Translabyrinthine Section of the Eighth Cranial Nerve. In Pulec, J. L.: Meniere's Disease. Philadelphia, W. B. Saunders Company, 1968, pp. 566-715. By permission of the publisher.)

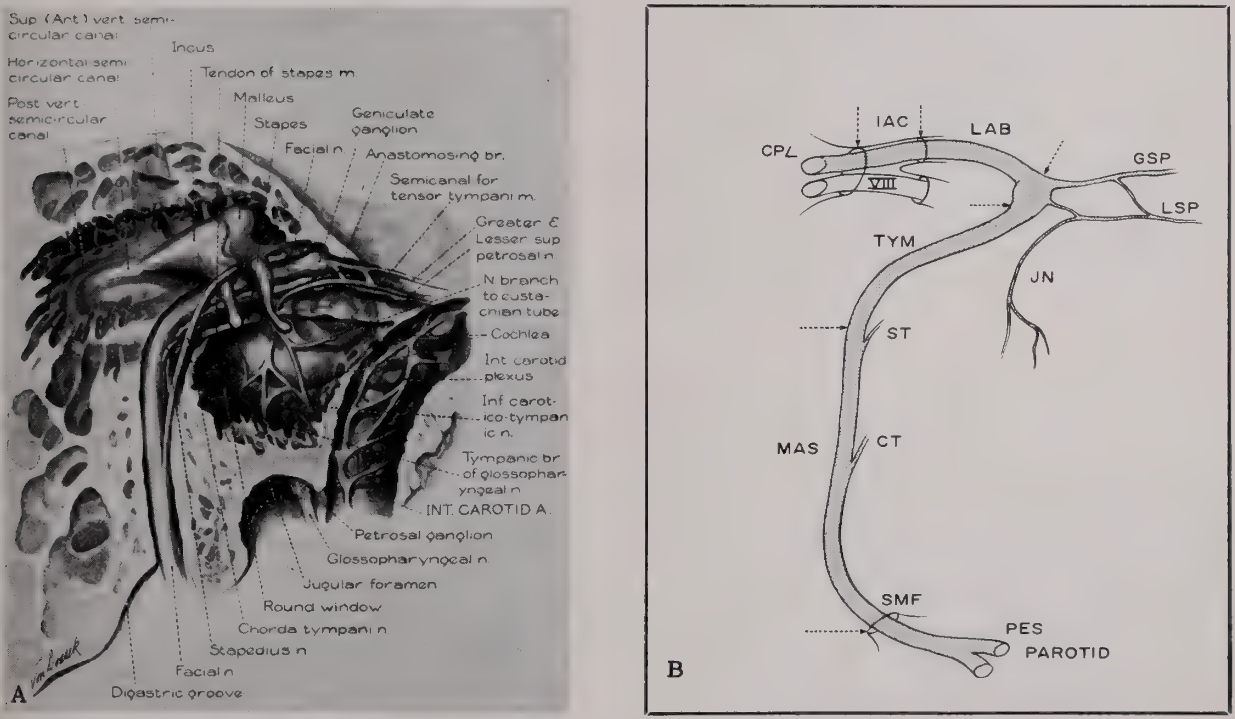
Sup (Ant) vert semicircular canal
Incus
Horizontal semicircular canal
Tendon of stapes m.
Post vert semicircular canal
Malleus
Stapes
Geniculate ganglion
Facial n.
Anastomosing br.
Semicanal for tensor tympani m.
Greater & Lesser sup petrosal n.
N. branch to eustachian tube
Cochlea
Int carotid plexus
Inf caroticotympanic n.
Tympanic br of glossopharyngeal n
INT. CAROTID A.
Petrosal ganglion
Glossopharyngeal n
Jugular foramen
Round window
Chorda tympani n
Stapedius n
Facial n
Digastric groove
A
IAC
LAB
CPL
GSP
VIII
LSP
TYM
JN
ST
MAS
CT
SMF
PES
PAROTID
B

Fig. 4—(A) Intratemporal course of facial nerve. (From Shambaugh, G. E., Jr.: Surgery of the Ear. Ed. 2, Philadelphia, W. B. Saunders Company, 1967, 722 pp. By permission of the publisher.) (B) Diagram of facial nerve: CPL = cerebellopontine angle portion, IAC = internal auditory canal portion, LAB = labyrinthine portion, GSP and LSP = greater and lesser petrosal nerves, respectively, JN = Jacobsen's nerve, TYM = tympanic portion, ST = stapedius branch, MAS = mastoid portion, CT = chorda tympani nerve, SMF = stylomastoid foramen, and PES PAROTID = beginning of parotid plexus.

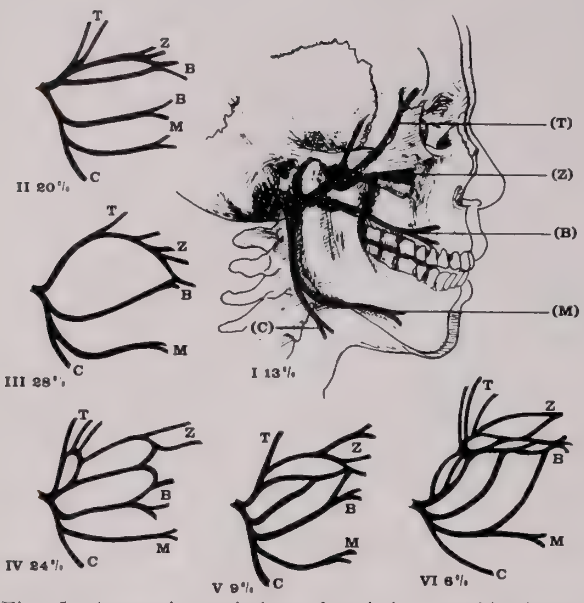

Fig. 5—Anatomic variations found in parotid plexus. (From Kettel, K.: Peripheral Facial Palsy: Pathology and Surgery. Springfield, Ill., Charles C Thomas, Publisher and Copenhagen, Munksgaard, 1959, 341 pp. By permission of the publisher.)

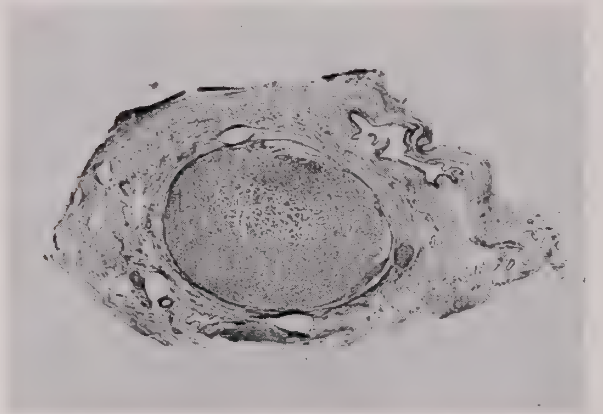

Fig. 6—Cross-section of facial nerve and its sheath in the mastoid portion. (Periodic acid-Schiff; x25.)

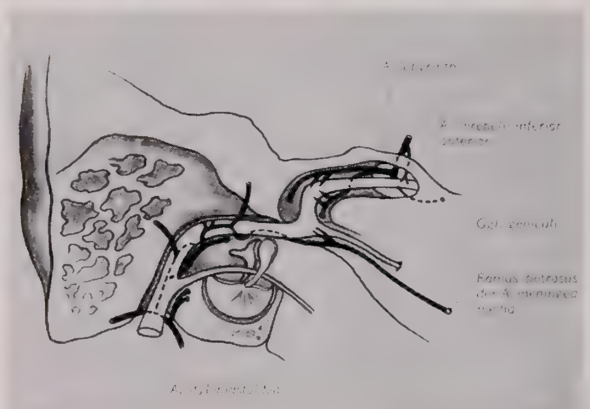

Fig. 7—Blood supply of facial nerve. (From Miehlke, A.: Die Chirurgie des Nervus facialis. München, Urban & Schwarzenberg, 1960, 208 pp. By permission of the publisher.)

Tympanic Portion

From the geniculum, the facial nerve arches downward on the medial wall of the aditus ad antrum between the stapes and the lateral semicircular canal. This is called the "tympanic portion" of the facial nerve. The facial nerve then curves slowly into the "mastoid portion" and descends vertically to reach the stylomastoid foramen. As the mastoid portion begins, the nerve to the stapedius muscle is given off, and at either the stylomastoid foramen or varying distances proximal to it, the chorda tympani nerve originates from the mastoid portion of the facial nerve and travels in its own bony canal toward the middle ear (Figures 4A and B).

The Three Branches

As the facial nerve leaves the temporal bone through the stylomastoid foramen, it gives off three branches: the digastric nerve to the posterior belly of the digastric muscle, the stylohyoid nerve to the stylohyoid muscle, and the postauricular nerve. The postauricular nerve is joined by the auricular branch of the vagus, as well as by branches from the greater auricular and lesser occipital nerves, and eventually innervates the occipitofrontalis and the auricular muscles.

The facial nerve then passes into the parotid gland anteriorly, where it forms the parotid plexus. Here the facial nerve divides into two major divisions, an upper zygomaticotemporal and a lower cervicofacial. These divide further into the five named terminal branches of the facial nerve. From above downward, these are the temporal, the zygomatic, the buccal (buccinator), the marginal mandibular, and the cervical. All the terminal branches anastomose with twigs of the fifth cranial nerve, except the cervical, which forms an anastomosis with branches of the second and third cervical nerves (Figure 5).

The facial nerve, of course, is responsible for the motor supply to all the muscles of expression, including the platysma. The exception is the levator palpebrae superioris muscle, which is supplied by the oculomotor nerve, explaining why the eye remains open in patients with complete paralysis of the peripheral facial nerve.

Histology

Similar to many other peripheral motor nerves, the facial is composed of bundles of fibers interspersed with connective tissue endoneurium and surrounded by the perineurium and epineurium. It is usual, however, to find the facial nerve consisting of only one large fiber bundle, with some very much smaller satellite bundles in the epineurium. Also, in the epineurium are found the vasa nervorum, which may be of considerable size. The perineurium and epineurium constitute the "nerve sheath," which fills about 50% of the fallopian canal (Figure 6). The nerve fibers occupy the remaining half of the canal. This nerve bundle is composed primarily of many myelinated fibers that range in size from about 1 to 14 μ. It is believed that the larger fibers are responsible for the transmission of motor impulses, whereas the smaller ones are the sensory and autonomic components. This belief is substantiated by the fact that the chorda tympani nerve and greater petrosal nerve are composed almost entirely of small myelinated fibers, which eventually form the nervus intermedius.

Blood Supply

The blood supply to the facial nerve (Figure 7) comes from the external and the internal carotid arteries, as well as from the vertebral system of arteries. The labyrinthine artery is a branch of either the basilar or, more usually, the anterior inferior cerebellar artery and supplies the preganglionic section of the nerve. This vessel does *not* anastomose with any of the other arteries. A branch of the external carotid artery, the posterior auricular artery gives off the stylomastoid artery, which enters the stylomastoid foramen and supplies the mastoid and some of the tympanic portion of the nerve. The petrosal artery, a branch of the middle meningeal artery, enters the middle ear space via the hiatus of the greater petrosal nerve and supplies the geniculum, the geniculate ganglion, and the remainder of the tympanic portion of the facial nerve.

There is a plexus of arteries, anastomosing on the promontory, that is primarily concerned with the blood supply to the middle ear, but occasionally may be involved in supplying the facial nerve. This plexus is composed of the posterior tympanic artery, a branch of the stylomastoid artery; the anterior tympanic artery, a branch of the maxillary artery; the caroticotympanic artery, a branch of the internal carotid artery; and the petrosal artery.

Summary

The anatomy of the seventh cranial nerve, as well as its histology and blood supply, has been reviewed.

Reference

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On Regimen in Acute Diseases

All diseases are resolved by the mouth, the bowels, the bladder, or some such organ. Sweat is a common form of resolution in all these cases.*

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*Hipprocates

Observe, record, tabulate, communicate. Use your five senses.—Osler

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The average man plays to the gallery of his own self-esteem.—Elbert Hubbard

Nobel Prize Winners in Medicine and Physiology

Wilhelm Einthoven 1924

For his discovery of the mechanism of the electrocardiogram

"The string galvanometer consists of a delicate thread, conducting electric current, stretched like a string in a magnetic field. As soon as the thread is electrified, it deviates from its equipoise in a direction at right angles to the direction of the magnetic lines of force. The magnitude of the deviation is proportional to the strength of the current flowing through the thread, so that this can be easily and exactly measured.

"Just as every muscle in its contraction generates an electric current, so also in the heart there is an evolution of electricity with every systole. . . . One needs only to lead the current from the hands and feet to the measuring instrument in order to see the variations in electric current, which show the same rhythm as the heart action.

"If one records the deviations of the measuring instrument one obtains a curve, which was called the electrocardiogram. But because of the imperfections of the capillary electrometer the curve directly recorded does not portray in an exact manner the actual variations in potential that have occurred. To get an exact picture one must construct a new curve based on the peculiarities of the instrument used and the data of the recorded curve, work requiring considerable time. This circumstance stood in the way of the practical application of electrocardiography to cardiac patients, and general interest in the ECG first developed later, after the string galvanometer made it possible to register the required pattern directly, easily, and quickly, and with satisfactory accuracy."

Einthoven first constructed a string galvanometer in 1903. From 1906 to 1921 he gradually improved it. By 1906 he had observed that different types of heart disease show different, and distinctive, tracings on the electrocardiogram. Between 1908 and 1913 he worked on the interpretation of the normal tracing, so as to provide a secure basis for the understanding of deviations from the normal result. His interpretation of each wave and complex in the recorded curve was worked out during this period, and the Prize was actually awarded not for the invention of the string galvanometer, but for the discovery of the mechanism of the electrocardiogram.*

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*Theodore L. Sourkes: Nobel Prize Winners in Medicine and Physiology, 1966.

What's Your Diagnosis?

A thirty-two-year-old white male, who was a heavy smoker, was employed in the taconite industry. For as long as he could remember, even prior to his smoking, he had had a rather noticeable cough, often productive of a small amount of yellowish sputum. This had not changed appreciably. Multiple chest roentgenograms had been taken because of his employment. Apparently these had all been considered "normal," although several times a second X ray was taken.

While attending a baseball game, he felt chilly and coughed up a small amount of bright red blood. Over the next few hours he coughed up approximately a cupful of bright red blood. He had no elevation of temperature and other than feeling rather weak and nauseated because of his constant coughing, he had no other particular symptoms.

What is your diagnosis? Turn to page 233.

Acute Suppurative Arthritis in Children

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THE GRATIFYING DECREASE in the mortality and morbidity of osteomyelitis and the mortality of joint infections as a result of sulfonamide, penicillin and broad-spectrum antibiotic treatment has not been followed by a comparable decrease in morbidity of joint infections. Wilkinson's[10] pessimistic view of 1952 is true today, "The story of infected hips has been written when the patient reaches us."

The reports of treatment of acute suppurative arthritis, particularly involving the hip joint, are very disappointing.[1]

Eyre-Brook[2] followed ten patients for five to 25 years and in 1960 reported uniformly bad results: capital epiphysis with persistent dislocation, one; loss of the capital epiphysis with residual neck in the acetabulum, one; loss of epiphyseal plate, two; coxa magna, four; gross osteomyelitis of the upper femur, one; no complications in only one patient.

In 1958 Samilson and co-workers[8] analyzed 35 cases of septic arthritis of the hip joint and reported the following complications: pathological dislocations in 10 out of 19 patients, coxa magna in three out of 19, osteomyelitis in nine out of 35 and spontaneous ankylosis in two patients. The few hips with good results had been treated by incision and drainage within four days of the onset of symptoms.

Obletz,[6] in 1960, reported suppurative arthritis of the hip in the neonatal period. The usual signs of fever, chills, swelling and prostration were not common. Typically the infant did poorly, refused to eat, was lethargic, had edema of the lower extremities and was febrile. Obletz advocated prompt surgical drainage.

In 1961, Ward, Cohen and Bauer[9] analyzed 21 cases of suppurative arthritis: 17 knees, two hips, one shoulder and one wrist. Four patients required surgical drainage; the rest were treated with aspiration and antibiotics.

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*St. Louis Park Medical Center, Minneapolis, Minnesota.

This study was supported by a grant from the St. Louis Park Medical Center Research Foundation, Minneapolis, Minnesota.

The results were better in patients treated one week or less after onset of symptoms.

The largest reported group of patients with septic arthritis is Gilmour's[3] of 1962: 27 cases of pyogenic arthritis of the hip joint and 11 cases of septic arthritis of the knee joint. His early results were poor; 15 out of the 27 hips ended with disastrous results despite either repeated aspiration of the hip or drilling alone of the femur; however, seven of his last eight cases did well with posterior arthrotomy through a three-fourth square inch capsular incision and irrigation.

The purpose of this report of 32 patients with acute suppurative arthritis is to show that early diagnosis and prompt aggressive treatment are the key to decreasing the joint destruction and consequent morbidity.

Pathogenesis

Hematogenous septic arthritis starts with implantation of bacteria borne by the blood from a distant focus to the metaphysis, the articulating socket or (rarely) the synovium (Figure 1-A). For practical purposes a septic arthritis may be considered a metaphyseal osteomyelitis with spread to the joint by rupture through the cortex. Alternatively, the infection can extend to the cortex outside of the capsule and become extra-articular or extend throughout the medullary canal to become a massive osteomyelitis.

The anatomy of the hip joint makes it vulnerable to this process: the epiphysis and metaphysis are completely intracapsular; the main vascular supply is comprised of the posterior inferior and posterior superior arteries which branch off the medial and lateral femoral circumplex artery; the epiphysis stays open until 16 to 17 years of age and the joint is deeper in location and surrounded by thick muscular and neurovascular structures which limit accessibility for treatment.

In contrast, the anatomy of the shoulder, knee and ankle joints resists such spread of infection. In these joints the metaphyses are extra-capsular so that prior to closure of the epiphysis, a suppurative process usually spreads to the cortex outside of the capsule to become a subcutaneous abscess or extends into the medullary shaft to become a diaphyseal and metaphyseal osteomyelitis (Figure 1-B). Such

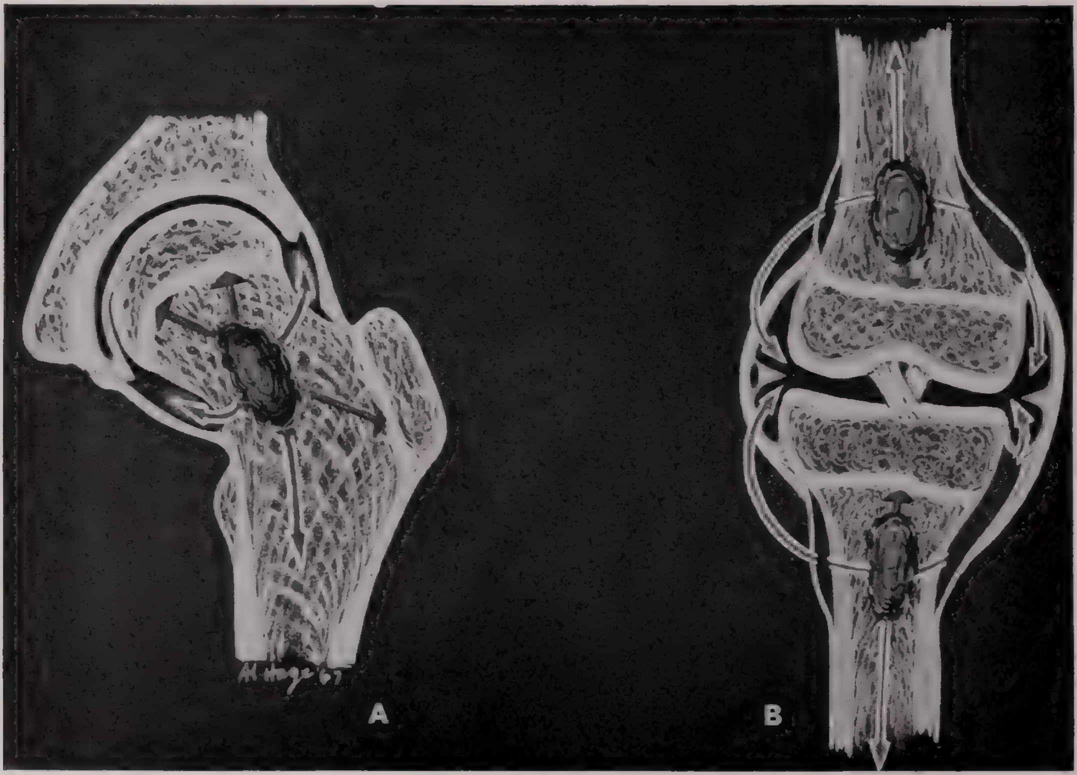

Fig. 1—Pathogenesis in septic arthritis.

infections rarely traverse the epiphyseal plate or epiphysis to break through the cortex and penetrate the capsule to gain access to the joint. However, when the epiphysis is closed, infection can spread directly into the joint. When infection has penetrated inside a joint, pus forms and the articular and subchondral cartilage is injured. Cartilage cell death is caused indirectly by a combination of nutritional failure and directly by injury from bacterial toxins.

Clinical Picture

The signs and symptoms vary with the severity of the infection, the etiologic agent and the patient's age. The typical clinical features observed in our 28 cases of septic arthritis were:

1. A very sick, toxic, miserable, irritable child who shouts, cries and resents any motion of the involved joint.
2. A temperature of 101 to 105° F.
3. A limp limb which the child will not use.
4. Localized bone tenderness.
5. Flexion deformity.
6. Leukocytosis and elevated sedimentation rate.

In constrast, the clinical picture in the neonatal infant is one of refusal to eat, lethargy, low hemoglobin and a gradually increasing temperature.

Regardless of age in the early stages (seven to 10 days), the x-ray is usually normal except for capsular distention. After two to three weeks, when the acute symptoms have subsided, bony x-ray changes such as mottling or periosteal elevation and layering are seen. Much later, sequestration develops.

Twenty-one patients were under 14 years of age, three under one year. Two out of five older patients had septic arthritis superimposed on rheumatoid arthritis.

The joints infected included 10 hips, nine knees, four ankles, two wrists and three elbows (Figure 2).

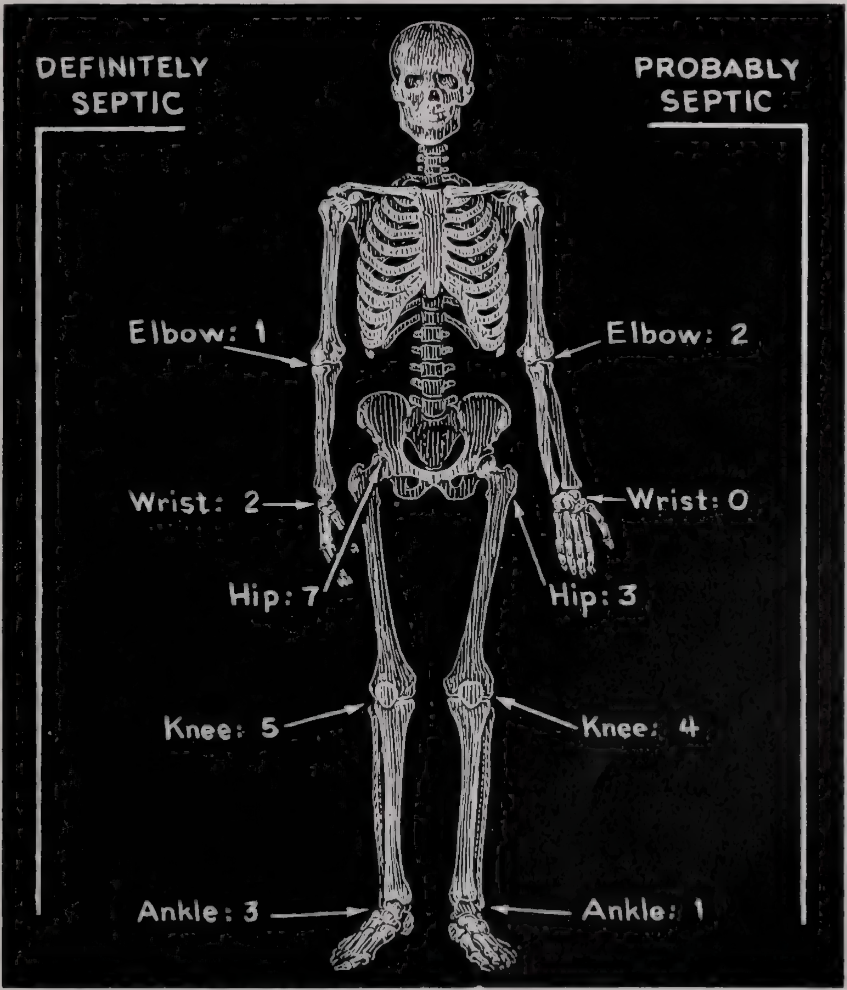

Fig. 2—Distribution of skeleton involvement in septic arthritis.

Twenty-seven patients (93%) had marked elevation of temperature and increased sedimentation rate. Leukocytosis (11,000-16,000) occurred in 20 patients (71%). Staphylococcus aureus was cultured from 13 patients. Six isolations were resistant to penicillin. Other bacteria found included Hemophilus influenza, Aerobacter, E-coli, Neisseria gonococcus and an unidentified gram-negative rod. Three patients with hip-joint involvement had positive blood cultures of Staphylococcus aureus coagulase positive.

Differential Diagnosis

Rheumatoid Arthritis

In acute juvenile rheumatoid arthritis more than one joint is usually involved. The synovium is inflamed and thickened with minimal effusion. Laboratory studies for rheumatoid factor and fluorescent antinuclear antibody are helpful if positive.

Toxic Synovitis

Toxic synovitis is quite common in the age group three to twelve years and is more common in boys. The common symptoms are pain in the hip with a limp. The temperature and white blood count may be slightly elevated. X-rays may show capsular distention. The acute symptoms may last three to five days. Suppurative arthritis can be excluded by aspiration and culture.

Rheumatic Fever

Rheumatic fever synovitis is part of a symptom complex which includes multiple joint involvement with erythema, carditis, abdominal pain, high sedimentation rate and positive C-reactive protein and a prior streptococcal infection.

Legg-Perthes Disease

Legg-Perthes disease synovitis presents as a limp with a vague onset followed later by typical x-ray findings in the head of the femur.

Hip-Joint Aspiration

The anterior approach is commonly used to aspirate the hip joint (Figure 3). Under sterile technique, the needle is inserted midway

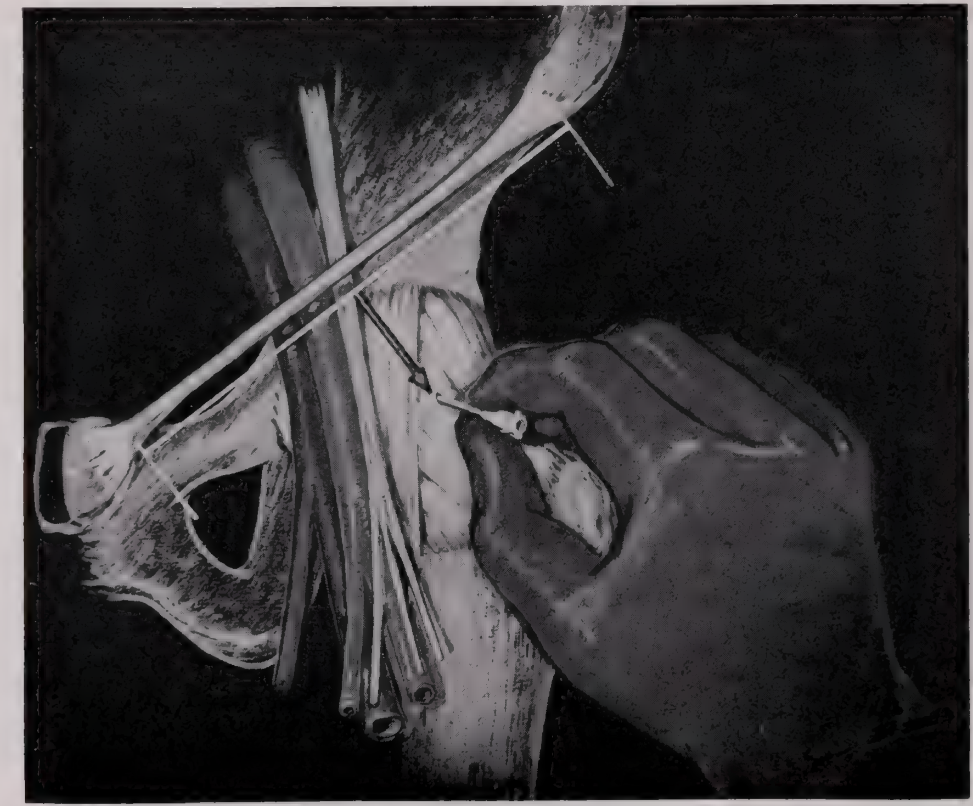

Fig. 3—Anterior approach of needle aspiration to the hip joint.

between the anterior-superior iliac spine and the symphysis pubis and directed 30 to 45° superiorly and medially. Procaine or xylocaine is infiltrated as the needle is directed with the index finger and thumb. The increased resistance felt as the needle reaches the joint capsule is followed by a giving-way sensation as the needle enters the joint. If no fluid is obtained by aspiration, entry into the joint can be checked by inserting the needle to touch bone. If the needle is touching the femoral head, it will move when the patient moves his leg. Alternately entry into the hip joint can be checked by injecting 3 to 5 cc of xylocaine and removing the syringe from the needle. If drops of xylocaine come out of the needle, the hip joint has been penetrated.

Analysis of 28 Cases

From 1960 to 1966, 34 patients were admitted to Methodist Hospital, Minneapolis, Minnesota, with monoarticular pain aggravated by motion and weight-bearing and the diagnosis of acute suppurative arthritis.

These patients were classified into three categories based on their entire clinical course and laboratory findings, including culture of the aspirated joint (Figure 2).

Definite Suppuration

In this group of definitely suppurative arthritis, there were 18 cases: patients who were sick on admission with severe pain and tenderness of the joint involved. They were highly febrile and had leukocytosis, increased sedimentation rate, and positive culture of the joint aspirate with or without positive blood culture.

Probable Suppuration

Probable suppuration was observed in ten patients. These patients had signs and symptoms identical with the first group except that culture of the joint aspirate was negative for any bacteria. The gross description of the aspirate was from very cloudy to sanguine-purulent.

Nonsuppurative

Nonsuppurative arthritis was obvious in six patients. These patients had a benign clinical course; two had nonspecific synovitis with no late sequelae, two had streptococcal arthralgia and two developed juvenile rheumatoid arthritis.

Our analysis will include only the first two groups of patients. The negative culture of the aspirate in Group 2 could be explained by treatment in about one half of the cases. Another probable reason for negative culture is that the fluid was aspirated early in the disease process when the reactive synovitis which precedes septic arthritis was present. Probably if the metaphysis had been drilled and cultured bacteriological identification might have been obtained. This was true in one patient whose joint fluid, although cloudy, was normal by culture, but in whom the aspirate from drilling the metaphysis revealed coagulase-positive Staphylococcus aureus.

Treatment

Twelve patients were treated by single or repeated aspiration and systemic antibiotics. Arthrotomy (open incision to the joint with Penrose drains or an irrigation-suction setup through the closed synovium) and antibiotics were used in 11 patients (seven hips, two knees, and two ankles), while drilling of the metaphysis was additionally used on three patients with hip disease.

Although all patients with septic arthritis of the hip were treated by arthrotomy, six were initially treated with large doses of intravenous antibiotics for two to five days without marked improvement.

Results of Treatment of Proven Septic Arthritis

Of the 18 patients with positive cultures, 16 were followed from six months to six and one-half years. Of the eight cases of septic arthritis of the hip joint, six were due to Staphylococcus aureus and two to Hemophilus influenzae. One was lost to followup. Five were normal clinically and had normal x-rays. One had fragmentation and avascular necrosis of the capital epiphysis; another had ankylosis of the hip joint with osteomyelitis and involucrum* of the proximal femoral shaft. These complicated cases followed infection by Staphylococcus aureus.

Other complications included asymptomatic narrowing of the wrist joint in one patient and of the ankle joint in another. A third patient had symptomatic marked narrowing of the subtalar joint. In two patients with rheumatoid arthritis, the residual of the infection was difficult to evaluate. To assess results of treatment of probable septic arthritis in the ten patients with a diagnosis of probable suppurative arthritis, seven were followed from one year to six years. Three were lost to followup. Seven were normal clinically and had normal x-rays.

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*See Test Your Word Score Page 265.

Discussion

This study confirms past reports of the dire consequences of delayed diagnosis and treatment of septic arthritis and emphasizes that early diagnosis and aggressive antibiotic and surgical treatment can prevent most late sequelae. To wait for roentgenographic evidence of suppurative arthritis, i.e., narrowing of the joint, periostitis and lytic changes of the metaphysis of the long bones which may not appear until three weeks after onset of symptoms, is to wait too long; for severe complications are common if treatment is delayed even one week after onset of symptoms.

Diagnosis

Effective early diagnosis must be presumptive and based on clinical (history, physical examination and laboratory studies) judgment. Alternating two-finger palpation and pressure helps localize bone tenderness and soft tissue swelling and warmth. Leukocytosis and increased sedimentation rate are usually present. When septic arthritis is suspected, the joint should be aspirated under sterile technique. Examination of the aspirate should include gram smear, aerobic and anaerobic bacterial cultures and sensitivity studies. Blood cultures should also be made. As soon as the cultures are done the patient should be started on massive doses of antibiotics.

Surgical Approach

Suction Irrigation

Aspiration and antibiotics are usually not effective in controlling the infection of the hip joint. Immediate arthrotomy, placement of a suction-irrigation setup and drilling of the metaphysis should be done when clinical history of suppurative arthritis of the hip is accompanied by a grossly purulent aspirate and a positive gram stain of the aspirate. A 24-hour delay of surgery may be permitted when the diagnosis is doubtful and bacteriologic culture is needed to confirm the diagnosis. The patient who is toxic from bacteremia frequently improves rapidly when surgical decompression is done.

The suction-irrigation setup is used for five days. Each day three to 4,000 cubic centimeters of an antibiotic solution is introduced into and then sucked out of the wound. Neomycin was once popular but should not be used if other antibiotics will suffice; for toxic effects on the kidneys with death have been reported. Penicillin and methicillin are currently recommended. Where changes of metaphysis and proximal femoral shaft are observed, a single spica cast should be applied.

Other joints, i.e., the knees, ankles and elbows, can frequently be treated effectively by repeated aspiration and massive doses of antibiotics. However, if the local signs and symptoms persist two to three days or increase, surgical decompression should be done.

Antibiotic Therapy

The staphylococcus is the etiologic agent in 70-80% of the positive cultures obtained from patients with septic arthritis. Streptococci (group A beta hemolytic, viridans and faecalis), clostridia and pneumococcal organisms are frequently found. Gram-negative bacteria including Hemophilus, Salmonella, Pseudomonas, Klebsiella aerobacter and coli-form organisms are infrequently cultured.

Antibiotic treatment should be delayed until aspiration and blood cultures are taken. Initial antistaphylococcal therapy should include penicillin and a penicillinase-resistant penicillin (Methicillin, oxacillin, nafcillin, cloxacillin or dicloxacillin). Methicillin is the preferred parenteral penicillinase-resistant penicillin because of serum-binding considerations, and cloxacillin and dicloxacillin are the best oral agents because of gastrointestinal absorption patterns. Parenteral administration is always preferred initially. Because of the increased incidence of Hemophilus influenzae infections in young children[11], ampicillin should be substituted for penicillin for children under age four years. If the patient is allergic to the penicillins, cephalothin, erythromycin or tri-acetyl-oleandro-mycin can be used. The initial antibiotic choices are necessarily subject to modification as the results of in-vitro antibiotic sensitivity testing become available.

After several days to two weeks of initial parenteral therapy, oral therapy is substituted. Antibiotic therapy should be continued until evidence of inflammation is gone and healing is manifested by x-ray examination, a period of one to 12 months.

Summary

An analysis of 32 cases of suppurative arthritis is presented, emphasizing the diagnostic signs, method of hip-joint aspiration, laboratory findings, x-ray findings early and late, and therapeutic regime. Suppurative arthritis of the hips offers special problems because of enclosure of the epiphysis and metaphysis in its capsule. In hip infection better results may be obtained by earlier diagnosis and arthrotomy. Infection of other joints may be managed by systemic antibiotics and repeated aspiration unless toxicity of the patient dictates surgical decompression of the joint. Antibiotic therapy should be directed initially against the staphylococcus and modified according to culture or gram stain of the aspirate results. Antibiotic therapy should continue until evidence of inflammation is gone and healing is manifested by x-ray examination.

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Shakespeare's Doctors

Dr. Caius

From the zenith of sublime tragedy and superb character delineation Shakespeare's versatile genius could descend facilely to the nadir of caricature and horseplay. In The Merry Wives of Windsor, Dr. Caius, the French doctor, contributes hilarity by his coarse accent and his rash impetuosity.

In love with Ann Page and learning that he has a rival in the person of Parson Hugh Evans, Caius challenges the parson to a duel, announcing in high dudgeon: "I vill cut his troat in de Park. I vill cut all his two stones; by gar, he shall not have a stone to trow at his dog."* (The vulgar among the audience must have howled at this pun.)

The duel never comes off, however. But Evans has the last word when he says of Caius: "He has no more knowledge in Hibbocrates and Galen,—and he is a knave besides."†

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*The Merry Wives of Windsor, I, 4.

†Ibid. III, 1.

It's the Law

Permitting Office Girl to Treat Patient Is Evidence of Doctor's Negligence

Evidence that a doctor permitted his office girl, a high school graduate with two years' experience as a nurses' aide, to treat a patient's lacerated hand on at least twelve occasions was held sufficient to send to the jury the question of the doctor's negligence, even in the absence of expert testimony. Accordingly, the Massachusetts Supreme Court overturned a lower court's directed verdict for the doctor.

The patient had consulted the doctor after injuring his hand at work. The doctor bathed the hand, gave pencillin and antitetanus injections, and prescribed medication for relief of pain.

When the patient returned to the doctor's office two days later, he was treated by the doctor's office assistant, who removed the bandage, soaked and bathed the hand, and rebandaged it. She instructed the patient to return to the office two days later. He did so and was treated by the doctor, who found that the thumb was swollen and that the flesh around the stitches was swollen and infected.

For more than a month the patient continued treatment, visiting the doctor's office a total of seventeen times. On no more than four of the visits was he seen by the doctor, being treated on the other occasions by the office assistant. She removed stitches, squeezed pus out of the thumb, prescribed pills, injected penicillin, removed and reapplied bandages, even advised the patient as to the treatment to be followed.

In the patient's suit against the doctor for malpractice, there was no expert testimony that the doctor was negligent in his treatment of the patient. However, the court said that there was sufficient evidence from which the jury could have found that the doctor did not use his best judgment in order to produce a good result. One basis for such a finding was the patient's testimony that the doctor failed to prescribe hospitalization, even after it was clear that the patient's thumb was infected. Another basis was the action of the doctor in permitting the patient to be treated by his office assistant to the extent described. The court concluded that the jury would be warranted in finding, without the aid of expert opinion, that the doctor's treatment of the patient was not consistent with standard medical practice.

Delaney v. Rosenthall, 196 N. E. 2d 878 (Mass., March 4, 1964)

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Is our oldest human relations tool (praise) really a psychological piece of candy? —Harvard Business Review

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Politician: An animal who can sit on a fence and yet keep both ears to the ground—Anonymous

* * *

A conservative is a man who does not think that anything should be done for the first time.—Frank Vanderlip

Abdominal Aortic Aneurysm Eroding into Duodenum

Pain at Unusual Site and Death from Gastrointestinal Hemorrhage

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Rochester, Minnesota

THIS CASE IS reported because of its unusual interest. First, the slowly progressive pain and loss of weight and strength, suggestive of malignancy, raised the question predominantly of either carcinoma of the pancreas or retroperitoneal lymphoma. Second, the intermittent and progressive nature of the pain confined to the lower part of the abdomen and lower part of the back as represented in this case seems a bit unusual for aneurysm of the upper part of the abdominal aorta. Finally, the case illustrates the importance of early exploration since, if this patient had undergone abdominal exploration prior to the fatal hemorrhage, the chances are fairly good that resection of the aneurysm and substitution of a graft might have saved his life.

Report of Case

A 64-year-old unemployed man came to the Mayo Clinic on March 4, 1963, because of intermittent but increasingly frequent pain that he had had in the lower part of the abdomen, scrotum, and lower part of the back since December 1962. The pain had begun in the lower right abdomen, over the right iliac crest, and across the lower lumbar region, initially on the right and subsequently also on the left. At first it occurred about every three to four hours. It was not, he said, a bowel cramp, and there was no history of peptic ulcer features. The pain was not affected by defecation or urination or by coughing, sneezing, or bending. It was worsened by sleeping on the right side. It interfered with sleep, causing the patient to sit up in a chair at night, as he felt somewhat better sitting up than lying down. When he was admitted some three months after the beginning of the illness, the pain was awakening him one to three times each night and was occurring during more of the day and the night than at the beginning. He obtained some relief while lying prone on his suitcase cushioned by a pillow. Associated symptoms were anorexia, loss of strength, despondency, increased flatus, and loss of more than 26 lbs in six to eight months. In 1960 he had had a myocardial infarction; since then he had been taking 5 mg of warfarin (Coumadin) daily.

Physical Examination

On physical examination the patient weighed 179 lbs

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*Mayo Clinic and Mayo Foundation: Section of Medicine.

His blood pressure was 140/80 mm Hg, pulse rate 108/min, and temperature 98.2 F. There was a grade 2 systolic murmur over the apex of the heart and over the second interspace near the right sternal border, but no audible bruit over the abdomen and no palpable masses. There was tenderness to pressure in and just above the right groin and over the region of the inguinal canal, but there were no masses or hernias. The prostate was enlarged (grade 1) and benign. There was tenderness to percussion over the third lumbar vertebra.

Neurologic Findings

Neurologic findings were essentially normal except for some decrease in vibratory perception about the knees and ankles and over the iliac crests.

Laboratory Analysis

Analysis of the urine showed red and white blood cells and hyaline casts (grade 1) with occasional granular and leukocytic casts. The specific gravity was 1.019. There was 10 ml of residual urine. The hemoglobin concentration was 12.5 gm/100 ml of blood, the leukocyte count 11,800/cu mm, and the sedimentation rate 77 mm in one hour (Westergren method). Values for serum bilirubin, acid and alkaline phosphatase, and blood urea, and the serologic reaction for syphilis were normal. The concentration of fasting blood sugar was 108 mg/100 ml (normal 65 to 90 mg). The prothrombin time (Quick) was 21 seconds. The sulfobromophthalein test of hepatic function showed that 8% of the dye was retained at the end of one hour. X-ray examination of the chest and excretory urography revealed no abnormalities. Proctoscopic examination for a disstance of 24 cm showed only hemorrhoids. X-ray examination of the lumbar spine disclosed hypertrophic changes with calcification confined to the lower abdominal aorta without widening. Subsequent review of the films provided no evidence of aneurysm. X-ray studies of the colon with the aid of barium showed diverticulosis in the region of the sigmoid. The terminal ileum was normal. An electrocardiogram showed the scar of an old infarct, the Q waves in leads 2 and 3 being lengthened with the S wave in lead 1.

Diagnostic Possibilities

It was felt that this could be a case of carcinoma of the pancreas in which pain had begun in the lower part of the abdomen and had not progressed far enough to be felt in the upper part. Besides, he had hyperglycemia with a negative family history of diabetes. A test of pancreatic function was performed with secretin (Vitrum), 1 unit/kg of body weight, given as a stimulus after the patient had fasted all night. The tip of the drainage tube was at the junction of the second and third parts of the duodenum as evidenced by a simple roentgenogram of the abdomen prior to starting the test. Constant suction of gastric and duodenal contents was carried out for one hour after stimulation with secretin. The test indicated an abnormally low volume (less than 1 ml/min) of secretion with essentially normal bicarbonate content, findings quite compatible with those noted in patients with pancreatic carcinoma.

It was felt that the abdomen should be explored, the most likely lesions being, in order, retroperitoneal lymphosarcoma or carcinoma of the pancreas. The surgeon who saw the patient concurred in this view. The patient did not wish to have the operation then, decided that he might return later, and was dismissed on March 14, 1963.

The home physician wrote that on March 20 (six days after dismissal from the Mayo Clinic) the patient had been hospitalized because of acute upper gastrointestinal hemorrhage with shock. The blood pressure was unobtainable and the pulse was weak and thready. The prothrombin time (Quick) on March 21 was 16 seconds.

The patient passed large quantities of bright red blood by rectum as well as vomiting copious amounts. The blood pressure gradually rose to 80/68 mm Hg, where it remained stable until March 23 when it again fell to 0 and he was given 500 ml of blood. Following transfusion the blood pressure rose to 110 to 150 systolic and remained stable until March 25, when it began to fall. He was given another 500 ml of blood, after which the pressure rose to 90/58 and he said he felt well. Twenty-four hours later he had had no further rectal bleeding. He was given a routine back rub and was then placed on his back, following which his color suddenly changed markedly, he had severe dyspnea and muscular twitching, and died quickly.

Autopsy

According to the local pathologist, autopsy revealed the white scar of an old myocardial infarct near the base of the heart posteriorly, the left coronary artery being narrowed by atheromatous plaques. The abdominal aorta had become a fusiform aneurysm from just below the renal arteries to the bifurcation, being dilated to about 5 to 8 cm on cross section, with the anterior upper part of the aneurysm lying against and firmly adherent to the transverse duodenum. At the site of the adhesion the duodenum contained an ulcer measuring 4 by 4 cm, and in the base of the ulcer an opening measuring 6 by 2 mm communicated with the lumen of the aortic aneurysm. The aneurysm contained a layered thrombus through which had developed a channel leading to the ulcer. The stomach contained a large blood clot. The duodenum, jejunum, ileum, cecum, colon, and appendix contained blood and clots. The pancreas was normal in size and contour and the cut surface was not remarkable. Microscopically the pancreas was normal. The liver also appeared to be normal, as did the gallbladder. The spleen, adrenals, and kidneys were normal. The pathologist summarized the findings as (1) abdominal aortic aneurysm ulcerating into the transverse part of the duodenum and producing massive hemorrhage into the duodenum, (2) arteriosclerotic heart disease with old healed infarcts on the left, and (3) amyloid kidneys.

Comment

Just why this aneurysm was not palpable by the many physicians who had examined the patient, both at home and at the Mayo Clinic, is obscure. Perhaps the most logical answer would be that an aneurysm was not suspected. The aneurysm must have become larger and more extensive than that which presumably was present on March 14, since the calcification that was visible on roentgenograms of the lumbar spine some three weeks prior to death was in the lower half of the abdominal aorta and indicated no abnormal widening of the aorta at this level. The progressive, relentless pain extending to the back and being worse in recumbency, the weight loss, the anorexia, and the loss of strength suggested malignancy involving the retroperitoneal region. The limitation of pain to the lower part of the abdomen and to the lower lumbar and sacral region rather than the upper lumbar and lower thoracic region suggested that the lesion was most likely located at a level lower than the pancreas. Therefore, a possible retroperitoneal lymphosarcoma loomed high among the likely possibilities. Yet the newness of the hyperglycemia and the results of the secretin test compatible with pancreatic carcinoma could not be overlooked. The lowness of the site of pain is interpreted as being likely due to stimulation of nerve fibers at the root of the mesentery. The low secretory volume of the pancreas is unexplained but could have been related to interference with pancreatic outflow caused by pressure against the pancreas and duodenum by the aneurysm. Although the secretin test was done in the Gastrointestinal Research Unit by an experienced technician, the possibility that the results were due to laboratory error cannot be dismissed.

Acknowledgment

I am indebted to Dr. Robert Lanning, Hannibal, Mo., who referred this patient and provided information on subsequent developments, including the autopsy report.

Disease as Reprisal V

Why was Job afflicted with boils?

God doubted his faith and wanted attestation of his physical endurance and moral stamina, after Satan's taunt.

So went Satan forth from the presence of the Lord, and smote Job with sore boils from the sole of his foot unto his crown. (Job 2:7)

And Job's ordeal by boils continued unremittingly until God was finally mollified by Job's admission of God's transcendent power and authority and by his humble self-abasement.

I know that thou canst do every thing, and that no thought can be withholden from thee.

Wherefore I abhor myself, and repent in dust and ashes. (Job 42:2, 6)

He must have had a magnificient build before his stomach went in for a career of its own.—Margaret Halsey

Quackery

Fundamentally, quackery is what quackery does. Kenneth L. Milstead, a Food and Drug official, employed this concept in seeking to mark the border beyond which quackery lay.

"When," said Dr. Milstead, "an untrue or misleading health claim is deliberately, fraudulently or pretentiously made for a food, drug, device or cosmetic, this is quackery. . . .

"It matters not whether the quackery is practiced by the witch doctor or the licensed medical practitioner; the Indian medicine man or the pharmacist; the proprietary drug manufacturer or the clerk in the health food store; the health lecturer, the self-styled nutritionist, the doorstep diagnostician, the fly-by-night operator or some of our most respected food, drug, device and cosmetic manufacturers—it is still quackery.

"It matters not which mask it wears—ignorance, superstition, fear, gullibility, folklore, myth, half-truth, or falsehood—it is still quackery.

"And it matters not whether the article is harmless or whether it gives some psychosomatic relief; whether it is cheap or whether it has value for other purposes; whether it is produced by an obscure firm or whether it is produced by a 'reputable' firm—the promotion of it is still quackery."*

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*James Harvey Young: The Medical Messiahs, 1967.

Of the Epidemics — Case I

Philiscus, who lived by the Wall, took to bed on the first day of acute fever; he sweated; towards night was uneasy. On the second day all the symptoms were exacerbated; late in the evening had a proper stool from a small clyster; the night quiet. On the third day, early in the morning and until noon, he appeared to be free from fever; towards evening acute fever, with sweating, thirst, tongue parched; passed black urine; night uncomfortable, no sleep; he was delirious on all subjects. On the fourth, all the symptoms exacerbated, urine black; night more comfortable; urine of a better color. On the fifth, about mid-day, had a slight trickling of pure blood from the nose; urine varied in character, having floating in it round bodies, resembling semen, and scattered, but which did not fall to the bottom; a suppository having been applied, some scanty flatulent matters were passed; night uncomfortable, little sleep, talking incoherently; extremities altogether cold, and could not be warmed; urine black; slept a little towards day; loss of speech, cold sweats, extremities livid; about the middle of the sixth day he died. The respiration throughout, like that of a person recollecting himself, was rare, and large, and spleen was swelled upon in a round tumor, the sweats cold throughout, the paroxysms on the even days.*

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*Hippocrates

Physical ills are the taxes laid upon this wretched life; some are taxed higher, and some lower, but all pay something.—Lord Chesterfield

Some people think that doctors and nurses can put scrambled eggs back into the shell.—Dorothy Canfield Fisher

Open Heart Surgery in Elderly Patients*

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OPEN HEART SURGERY can be performed safely in elderly patients. With careful selection, application of current refinement in bypass technique, and assiduous attention to technical detail, patients even in the eighth decade can receive substantial functional improvement from these procedures. We have operated upon four patients whose ages ranged from 71 to 79 years for both valvular and congenital cardiac lesions. All survived and are currently living and improved.

Case Reports

Case 1

A 75-year-old male with severe calcific aortic stenosis. Functional class III, atrial fibrillation and repeated bouts of congestive heart failure, grade II aortic systolic murmur.

Chest X-Ray and Cardiac Fluoroscopy: Cardiomegaly with left ventricular contour, heavily calcified aortic valve.

Electrocardiogram: Atrial fibrillation, left ventricular hypertrophy.

Cardiac Catheterization: 50 mm. gradient across the aortic valve with a cardiac output = 2.4 L/min (index).

Surgery: Heavily calcified aortic valve replaced with a Cutter prosthesis.

Postoperative Course: Uncomplicated. Dismissed on the 11th postoperative day.

Case 2

A 71-year-old female, functional class IV. Severe mitral incompetence, pulmonary hypertension, marked tricuspid incompetence, grade IV holosystolic apical murmur and grade III systolic murmur along the lower right sternal border. Marked neck vein distention. Liver enlarged and pulsatile.

Chest X-Ray and Cardiac Fluoroscopy: Cardiomegaly with marked right and left atrial enlargement, no valvular calcification.

Electrocardiogram: Atrial fibrillation.

Cardiac Catheterization: Aortic valve normal, confirmed severe mitral incompetence, pulmonary hypertension (pulmonary artery pressure—110/38), marked tricuspid incompetence.

Surgery: Mitral valve repair, tricuspid annuloplasty.

Postoperative Course: Slow convalescence, no specific complications. Dismissed on the 22nd postoperative day.

Case 3

A 79-year-old female with acute onset of severe mitral insufficiency four months prior to admission. Functional class IV, atrial fibrillation, dyspnea, orthopnea, hepatomegaly and peripheral edema. Grade IV apical holosystolic murmur.

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*See editorial page 261.

Chest X-Ray and Cardiac Fluorescopy: Cardiomegaly, left atrial enlargement, no valvular calcification.

Electrocardiogram: Atrial fibrillation.

Cardiac Catheterization: Confirmed clinical findings of severe mitral incompetence. Aortic valve normal.

Surgery: Ruptured chordae, anterior leaflet of mitral valve. Valve replaced with a Cutter prosthesis.

Postoperative Course: Complicated by recurrent bouts of fluid retention. Dismissed on 47th postoperative day.

Case 4

A 76-year-old female. Secundum atrial septal defect, functional class IV, grade III systolic ejection murmur in the left third interspace.

Chest X-Ray and Cardiac Fluoroscopy: Enlarged pulmonary artery, right ventricular enlargement.

Electrocardiogram: Incomplete right bundle branch block.

Cardiac Catheterization: 60% left to right shunt at atrial level. Cardiac output = 1.75 L/min (index). Pulmonary artery pressure 54/18.

Surgery: Repair of large secundum atrial septal defect.

Postoperative Course: Developed rapid atrial fibrillation, attempt at cardioversion unsuccessful. Rate controlled with digitalis. Slow but steady improvement. Dismissed on 48th postoperative day.

Discussion

When hemodynamically correctable heart disease is present in the elderly patient and is the major factor limiting activity, then age should not be considered a contraindication to cardiac surgery.

The diagnosis of the lesion in question can be ascertained with a high degree of accuracy using the standard techniques of palpation and auscultation, cardiac fluoroscopy and electrocardiography. When necessary, cardiac catheterization can be accomplished safely.

While the conduct of extracorporeal circulation is essentially the same regardless of age, errors in technique, resulting in inadequate coronary perfusion, excessive hemolysis, inadequate systemic flow, and air embolism may be particularly devastating when they occur in the elderly.

Severe, acquired multiple valve disease does occur in the elderly patient; however, calcific aortic stenosis and mitral valve disease as isolated lesions are more common. Complex forms of congenital heart disease are rarely encountered. Age adds a peculiar feature affecting the risk of surgery in each of these more common lesions and merits separate attention.

Calcific Aortic Stenosis

This diagnosis is generally suspected in the patient who has symptoms of angina, syncope, or dyspnea, and who is found to have an aortic systolic murmur. Confirmation rests on the electrocardiographic evidence of left ventricular hypertrophy (in the absence of significant hypertension) and the finding of a heavily calcified aortic valve by fluoroscopy. In the typical case, further laboratory study is unnecessary. In the elderly patient, however, trivial aortic stenosis or valvular sclerosis may give rise to aortic ejection murmurs. Voltage criteria for ventricular hypertrophy may be absent, due to the decline with age of the voltage of the QRS complex. ST and T wave abnormalities also become less specific. The symptoms of syncope must be distinguished from Stokes-Adams attacks and extracranial vascular occlusive disease. Confusing findings indicate the need for appropriate laboratory study.

The risk of aortic valve replacement in the elderly is altered by the technical difficulty which may be encountered in suturing an aortic wall which is thin and damaged by arteriosclerosis. Re-bleeding in the early postoperative period from the aortotomy continues to be the most worrisome feature in this operation. It is doubtful that coronary artery disease significantly contributes to the risk of aortic valve replacement when associated with severe aortic stenosis.

Mitral Valve Disease

Surgery for acute mitral insufficiency resulting from ruptured chordae can be expected to produce good hemodynamic results. Often valve replacement is not required. The lungs have not been damaged by chronic pulmonary venous hypertension and can be expected to have near normal compliance. Age is clearly not a deterring factor toward surgical repair.

When the lungs have been exposed to chronic pulmonary venous hypertension for many years, and severe pulmonary artery hypertension is associated with right ventricular dilatation and tricuspid incompetence, the risk of surgery may be high regardless of age. Chronic right ventricular failure (with pulsating neck veins and hepatomegaly) is a late and needless complication. Pulmonary vascular obstruction and atrial fibrillation, repeated pulmonary emboli and, rarely, associated organic tricuspid disease may be factors in its development. All of these may be present simultaneously, and the relative importance of each may be difficult to assess. The extent to which these factors are reversible or lend themselves to repair largely determines the outcome of the surgical procedure. There may be some patients with long-standing right ventricular failure who do poorly after surgery because of a *dominant "myocardial factor."* More often, however, this diagnosis conceals diagnostic or technical error and is used as an excuse for failure to improve following surgery. Certainly in the preoperative evaluation, this diagnosis should never be made except by the most rigid process of exclusion.

Recognizing that the greatest risk of mortality in this group of patients is "low cardiac output" in the early postoperative period, we favor a plastic repair of the valve when possible. The elderly patient does not require a perfect hemodynamic result in order to be improved sufficiently to allow sleep in the recumbent position and to avoid dyspnea with the level of activity consistent with his age.

Although the postoperative recovery period was prolonged in each of these mitral valve patients (22 and 47 days respectively), the final result was gratifying. Fluid retention in the late postoperative period, which often accompanies mitral valve surgery in functional class III and IV patients, was a problem in only one case.

Atrial Septal Defect

Atrial septal defect repair in the elderly can be expected to provide good results if there is still a large left-to-right shunt present. If, with many years of volume overload, the right ventricle has lost much of its distensibility so that the end diastolic pressure is elevated, preventing left-to-right shunting, then closure of the defect cannot be expected to be beneficial. The development of severe pulmonary hypertension with high pulmonary resistance may likewise mitigate against a favorable result. Short-term anticoagulation in the early postoperative period may be a worthwhile safeguard, since pulmonary embolism seems to be more common after atrial septal defect repair in adults.

Summary

Although the risk of surgery in potentially correctable cardiac lesions may be altered by age, proper selection and attention to technical detail can yield satisfying results. In this group of patients undergoing open heart surgery, whose ages ranged from 71 to 79 years, all are living and improved.

Answer to What's Your Diagnosis

(From page 218)

Bronchiectasis is one of the most common causes of hemoptysis. Although there are multiple other possibilities, this would be considered first with this history.

A Formula for Health

"The only way to keep your health is to eat what you don't want, drink what you don't like, do what you'd rather not."—Mark Twain

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IBM Perhaps

The aim of medicine is to prevent disease and prolong life; the ideal of medicine is to eliminate the need of a physician.—Wm. Mayo

Shakespeare and Medicine

The Hallucination of Lady Macbeth

Shakespeare's insight into the dark and secret depths of the guilty human mind was so phenomenal for his time as to make his grasp appear an intuitive endowment: an innate power derived from within rather than acquired from without.

His arresting portrait of Lady Macbeth in her sleep-walking scene is a masterpiece of dramatic impact and psychological penetration. Her usual poise and reserve shattered by morbid hallucinations generated by guilt and remorse, she walks about in nocturnal somnambulism, agonizing over imaginary and accusatory blood stains on her hands.

"Out, damned spot! out, I say!—Hell is murky!—Fie, my lord, fie! a soldier, and afeard?—Yet who would have thought the old man to have had so much blood in him?"

That the doctor shrewdly assesses her condition is evident from his somewhat cryptic comments:

> "The heart is sorely charged."*
> "This disease is beyond my practice."*
> "Unnatural deeds do breed unnatural troubles; infected minds will to their deaf pillows discharge their secrets. *More needs she the divine than the physician.*"*

When Macbeth confronts the doctor later with the question: "How does your patient, doctor?" he answers:

> "Not so sick, my lord, as she is troubled with thick-coming fancies, that keep her from her rest."*

Whereupon Macbeath charges him:

> "Cure her of that. Canst thou not minister to a mind diseased, pluck from the memory a rooted sorrow, raze out the written troubles of the brain, and with some sweet oblivious antidote cleanse the stuffed bosom of that perilous grief which weighs upon the heart?"*

To which the doctor replies in seven words of apocalyptic dimensions that echo down the corridors of time:

> *"Therein the patient must minister unto himself."**

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*Macbeth Act V Scene 1

Mental Attitude

Carry your chin in and the crown of your head high, fill the lungs to the utmost; drink in the sunshine; greet your friends with a smile and put soul into every hand-clasp. Picture in your mind the able, earnest, useful person you desire to be, and the thought you hold is hourly transforming you into that particular individual.—Fra Elbertus

Flying Saucers

When it comes to flying saucers, some realists report that they can see saucers best when they are in their cups.—Harlow Shapley

Three Basic Brain Models

of the Last Three Centuries

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THE CONCLUSIONS which Galileo and Newton applied to mathematics and physics three to four centuries ago had direct and dramatic influence on the model of the universe which was accepted at that time. The result was a refutation of the Ptolemaic theory of astronomy. The secularization of science was vigorously opposed because it appeared to refute the basic assumption of theology: namely, that the existence of the universe and the development of man were the direct result of an act of intention by a divine person. The increased sophistication regarding energy forces and cause-effect mechanisms appeared to diminish the probability that the intention of an anthropomorphic god could account for the existence of man in the universe. The response in the 19th century to Darwin's theory of evolution revealed quite clearly that secular science was seen as being in opposition to the theory of divine intention.

Application of these concepts of a non-intentional or "mechanical" cause-effect relationship in biology has been a gradual one until the 20th century. These changes can be illustrated by the consideration of three brain models, representing each century's biologic and secular answers to questions regarding motion, emotion, and intention behavior.

The first model is based on a simple hydraulic theory; the second represents a much more sophisticated understanding of anatomy. The phylogenetic brain model of the 20th century is both descriptive and useful, since it has led to more questions than it "answers."

The Brain Model of the Middle Ages

The first brain model appears to have answered questions and satisfied curiosity for about 1400 years. This can be called the "Vital Fluid" model. The energy theory which it used was probably developed when the Roman Empire mastered the techniques of building and using aqueducts. These concepts were employed by Galen in the 2nd century A.D. In this brain model, the nerves were believed to be hollow and filled with fluid. Disturbance of a nerve altered the dynamics of fluid in the ventricles of the brain, releasing some vital "animal spirits," which would flow to muscles and cause activity. This was basically the brain model of Descartes when he published "Traite de l'Homme" in 1664. The analogy he used was drawn from hydraulically activated dolls which were popular among the aristocracy of the time. The value of Descartes' proposals lies not in his answers but in the fact that he dared to approach the questions at all. His conclusion expressed the dissatisfaction of the era with the mythology of devils, evil, and witchcraft which had been dominant for so many centuries. The model he proposed was an ancient one; yet the implicit rejection of supernatural forces in biology left his successors free to search for more sophisticated answers.

The Brain Model of the 19th Century

The succeeding 150 years brought a high degree of sophistication about the central nervous system, although primarily in anatomy rather than physiology. In 1800, Xavier Bichat published an extensive review regarding brain anatomy and behavior: a work which revolutionized the teaching of gross anatomy and was accepted as dogma for over a century. With regard to the nervous system he identified two great complexes: one arising from the autonomic ganglia and the other from the brain and spinal cord. He clarified the anatomic separation of the autonomic and somatic nervous systems. His conception of the origin of emotions was his point of continuity with the past; he believed that emotional experience began in the organs of the body, rather than being projected to them. This was demonstrated in the association of heart activity with anger, sobbing and respiration with grief, and stomach distress with resentment.[1]

While Bichat's conclusions were both brilliant and revolutionary, their acceptance as medical dogma in the 19th century served to dampen curiosity and inhibit the understanding of emotional responses and behavior. Curiosity, which is stimulated by incomplete answers, is often stifled by dogmatic conclusions. It is paradoxical that Sigmund Freud, whose theories based on clinical observations were to revolutionize psychology in the 20th century, accepted this idea that visceral symptoms were not psychological in origin. He concluded that hysterical symptoms involving the cerebrospinal nervous system could be used as symbolic resolutions of psychic distress. However,

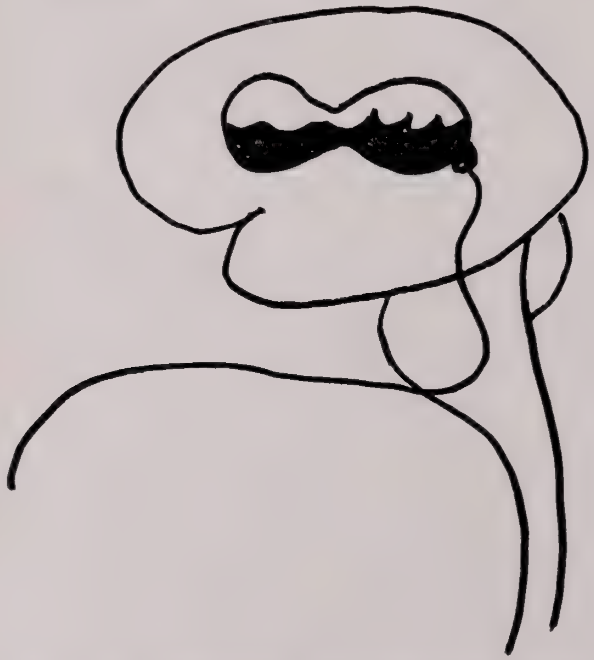

Fig. 1—The "Vital Fluid" Brain Model of the Middle Ages from Galen to Descartes.

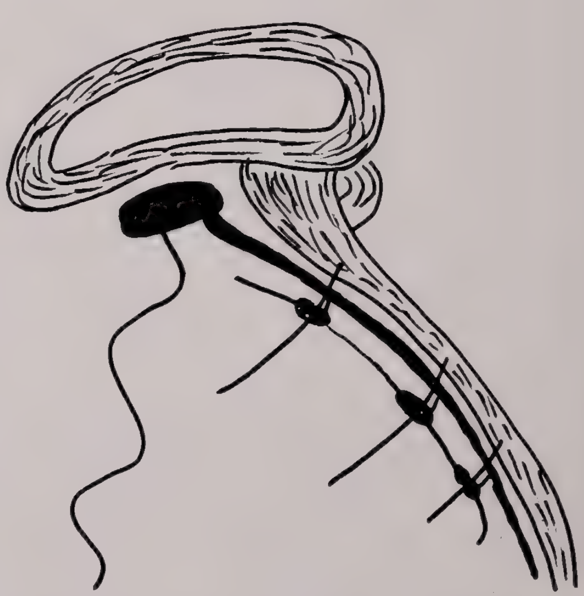

Fig. 2—The 19th Century Brain Model of Bichat, Composed of Two Independent Systems.

he saw the ganglia or "little brains." of the automatic system as being independent. This illustrates that he was a 19th century genius who increased the freedom of 20th century thought, and that, like Bichat's, his propositions should not be projected into dogma.

The Brain Model of the 20th Century

At the end of the 19th century studies in comparative anatomy presented biology with a new conception of the brain as an organ which showed progressive development and enlargement during the course of evolution. While the spinal cord and brain stem were seen to be structurally consistent among vertebrates, mammalian development proceeded by adding new structures to the basic, primitive brain. Hughlings Jackson expressed this when he proposed that the highest brain centers which developed last in the course of evolution impose discrimination and control over the primitive behavior of the lower centers.[2] Drive behavior involving feeding, fighting, flight, and sexual arousal are certainly pre-mammalian in development. The higher centers influence activation, direction, and inhibition of these primitive drives which will have focal centers in the structures directly associated with the brain stem.

Visceral Brain or Limbic System

An important elaboration of this concept was proposed by C. Judson Herrick in 1933. The structures of the rhinencephalon or "nose brain" had been found to be anatomically related to the olfactory nerve and behaviorally related to the sense of smell involving feeding, searching, avoidance, and sexual behavior. On the basis of extensive comparative studies Herrick found that this system included the ancient cortex of early evolution and was integrated with the hypothalamus at the top of the brain stem.[3] He therefore concluded that this system served as a non-specific activator for all cortical activities, either exciting or inhibiting such functions as memory, learning and affect. Papez in 1937 proposed a reverberating circuit for emotional experience within this system which has subsequently become the basis for a large amount of productive research.[3]

Paul MacLean has reviewed the studies of this system and, in calling it the "visceral brain," has emphasized its important influence upon the automatic nervous system and psychosomatic disease. He later pointed out that these structures had been called the "limbic lobe" by Broca in 1878, since the rhinencephalic structures became a "limbus" or border for the cerebral peduncles as evolution proceeded with the development of the neocortex.[1] When MacLean summarized the conclusions of Herrick regarding the integration of the olfactory apparatus of fishes and reptiles, with the developing hypothalamus, he concluded that the brain stem and spinal cord constituted a "neural chassis" for behavior. With the addition of this system and its hypothalamus to direct choices and select behavior, evolution had added a "driver at the wheel of the neural chassis." This articulate description illustrates that the brain model of the 20th century is one which emphasizes both activation and inhibitory mechanisms, both of which are essential for selecting behavior.[4]

Phylogenetic Brain Model

In 1962 Paul MacLean proposed an apt and simple description of these brain systems which can provide the basis for the brain model of the 20th century. He observed that nature has endowed man with essentially three superimposed and integrated brains.[5] The most primitive is the "reptile brain" comprised of the spinal cord and brain stem with its motor nuclei of the autonomic nerves and the nonspecific neurones of the reticular system. This is essentially the "neural chassis" he had mentioned previously. The next to develop was the "early mammalian brain" which consists of the visceral brain or limbic system and contains the hypothalamus and its circuits which became the "wheel" for the neural chassis below. The medial forebrain bundle of this brain can be said to separate into two circuits, one dealing with self-preservation and the other with species preservation. These brain systems are basically "non-literate" and must be integrated with the last system to develop, the "primate brain" of the neocortex, which contains the extensive tracts of the association areas of the cortex which Hughlings Jackson referred to almost a century ago as the "highest brain centers," which regulate behavior. This phylogenetic brain model is a capsule summary of the work of many investigators and provides a generalization within which many findings can be placed in psychobiologic perspective.

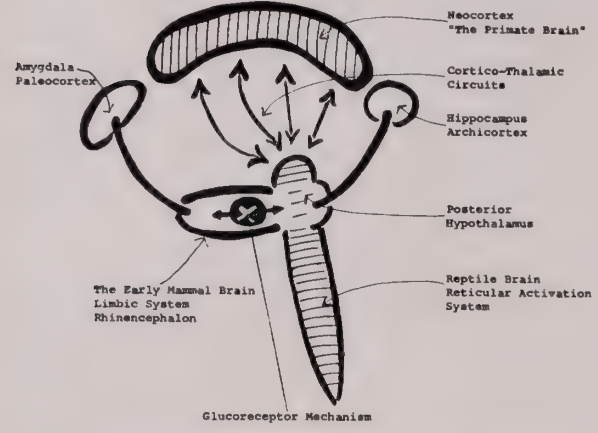

Fig. 3—The Phylogenetic Brain Model of MacLean and the 20th Century.

A Psychobiologic Summary

The study of man and his behavior during the past century has primarily been by two disciplines, physiology and psychology, which were principally concerned with objective phenomena and subjective experience. Physiology and psychology represent two viewpoints—two different levels of logical abstraction—which are concerned with the *same* biologic life process. Herrick has summarized this quite explicitly: "Psychology is a biologic discipline, but it should be a psychobiology and not merely a subdivision of physiology. What we must do now is to bring together these artificially separated domains of experience, the subjective and the objective, and build a coherently integrated psychobiology."[6]

Metabolic Requirements

The phylogenetic brain model provides a useful generalization which helps to organize data. Studies of the metabolic activity of the reptile and early mammalian brain systems have shown them to have less need for glucose in their functioning than the primate brain. On the other hand, their metabolic activity is greater at birth than the neocortex which has not yet matured to its normal adult physiologic capacity,[7] although the adult neocortex uses much more glucose.

Comparative Enzyme Systems

We would naturally expect that the enzyme systems of the reptile brain would be "primitive" compared with the neocortex of the primate brain, since the reptile brain will still function at temperatures which are much below those that the mammalian brain requires. This is confirmed in man by current work on hypothermia, since the brainstem structures maintain their functioning long after the structures above have been inhibited. The same findings were observed during the insulin hypoglycemic coma therapy treatment of schizophrenia. Brain stem nuclei maintain respiration and cardiac function during hepatic and renal coma when the activity of the primate brain has been inhibited.

Response to Drugs

These brain systems respond differently to barbiturate and to tranquilizing drugs. The principal neurophysiologic distinction between these drugs is that barbiturates depress activity in the primate brain, while the tranquilizers, in moderate doses, do not.[8] Moreover, when the barbiturates depress neocortical activity they allow an increased activity in the posterior sympathetic hypothalamus[9] where activation is associated with aggressive behavior. This can help to account for the disorientation and "temper tantrums" which senile patients so frequently have when given barbiturates. Since the neocortex of the primate brain is the first system to degenerate under the stress of aging, the addition of barbiturates which depress activity here has an additive effect and can increase the symptoms of senility.

Tranquilizing drugs do not inhibit the neocortex so readily. Also various tranquilizers differ markedly in their effects on key brain areas and thus vary in their therapeutic effect on human behavior.[8] In particular, chlorpromazine (Thorazine) depresses activity in the posterior hypothalamus of the early mammalian brain[9] and tends to diminish the impulsive aggressive behavior of the senile.

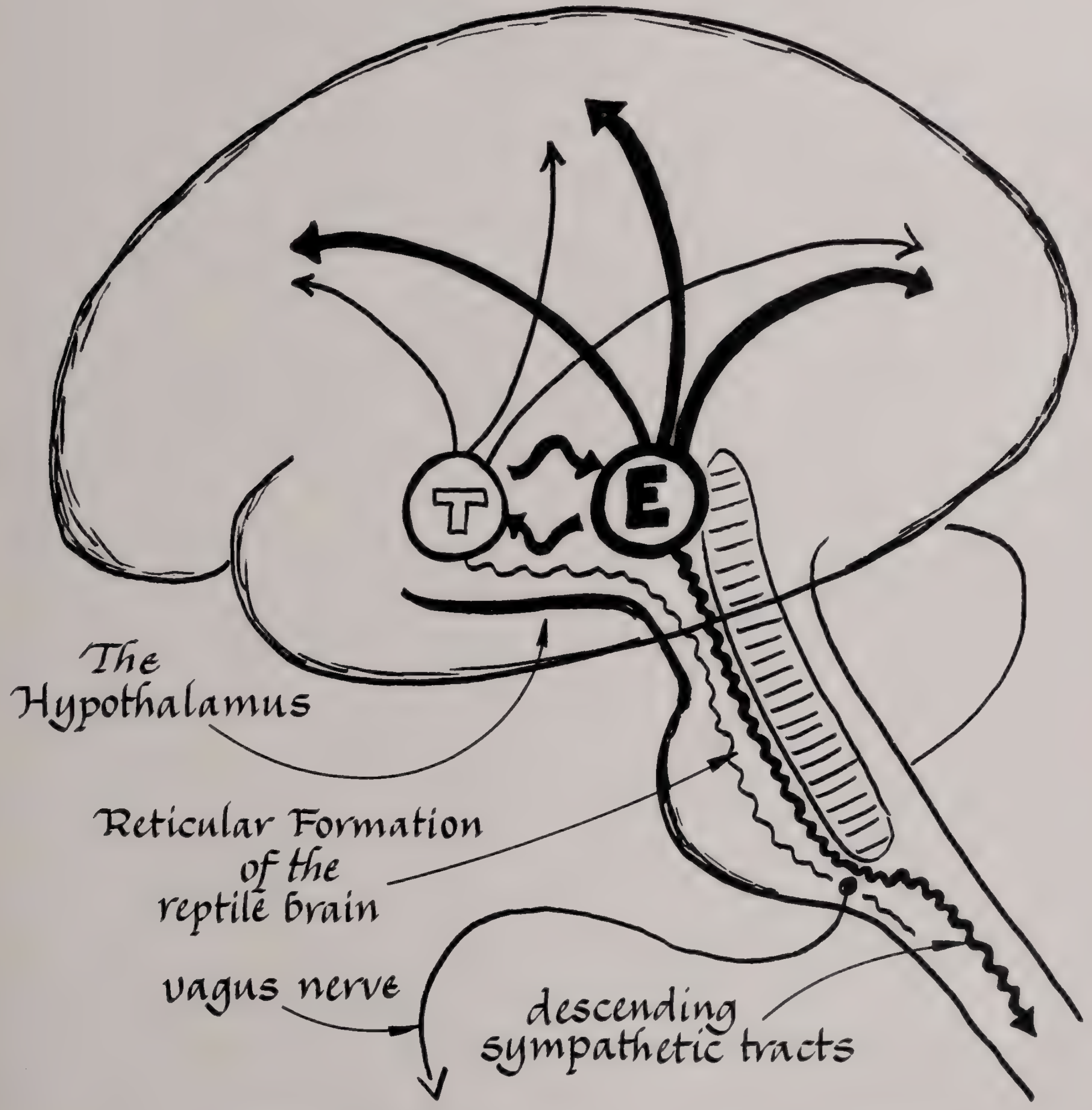
T
E
The Hypothalamus
Reticular Formation of the reptile brain
vagus nerve
descending sympathetic tracts

Fig. 4—The Gellhorn-Hess Physiologic Brain Model. Two action systems are represented here. The E-system is the ergotropic system and its pathways are represented with the heavy lines. Its descending "motor" tracts activate the sympathetic division. The T-system is the trophotropic system represented with lighter arrows. Its descending motor tracts activate the parasympathetic division of the autonomic nervous system. The major relay area for these systems is in the hypothalamus. One arrow between the T and the E nuclei here represents the process of "reciprocal inhibition" which functions during physiologically normal behavior. The other arrow represents "spill-over" of activation, since intense activation of one system can paradoxically activate rather than inhibit the other system. The "E"-system is dominant during the waking state.

Basis of Emotions

This phylogenetic brain model is obviously not intended as a blueprint for the complicated maze of positive and negative feed-back circuits of the brain. It provides a useful framework in which the development, location and function of circuits and systems can be described. The rhinencephalic circuits activated by the sense of smell were developed during the course of evolution to direct behavior related to feeding, fighting, flight, and sexual arousal. The integration of these circuits of the limbic system with the primate brain which eventually evolved provides the biologic basis for the experience which we now label "emotion."[10] The extensive studies of the neurophysiologic circuits involved in emotions and emotional disorders[11] now provide the basis for the psychobiologic study which Herrick saw as our next area of understanding: the integration of the objective and subjective domains of experience.

The Psychobiologic Conclusion

"Mind is not something acting on the body to make it go. It is the body in action. My mind is not something I have. It is something that I am. For I am a minding body."—C. Judson Herrick.[6]

Addendum

The phylogenetic brain model which has been proposed by Paul MacLean can also be called an "anatomic" model. The fact that these three systems are integrated in their function is accepted as an implicit fact. A physiologic brain model which begins to describe this anatomic model can currently be proposed. This physiologic brain model represents conclusions which correct the assumption of the Bichat model of the 19th century, that the somatic and autonomic nervous systems were independent of each other in their action. There are operant systems of entering sensory impulses which have connections with the reticular system in the "reptile" brain stem, as they proceed to sensory areas of the neocortex. There are ascending tracts to the hypothalamus which is an important relay center for circuits within the limbic system of the "early mammal brain," and which extensively influence the "primate brain" of the neocortex.

The hypothalamus which MacLean had called "the driver at the wheel of the neural chassis"[12] has been called "the hub of the limbic system" by Gellhorn.[13] It was called the "head ganglion" of the autonomic nervous system by Fulton in 1940, and its descending tracts regulate the motor cells of the autonomic nervous system in the brain stem and spinal cord. Activation of the ascending tracts from the posterior hypothalamus are associated with arousal of the cortex, and apparently uncomfortable, anxious or rageful behavior.[13] The downward tracts activate the sympathetic division, with increased blood pressure, pulse, and release of epinephrine. Activation of the anterior hypothalamic area is associated with cortical activity seen with sleep, and the downward tracts activate the parasympathetic division of the autonomic nervous system.

The balance and equilibrium of these divisions of the autonomic nervous system was the primary focus of Ernst Gellhorn for about thirty years. He concluded that the principle of "reciprocal inhibition" which Charles Sherington had proposed to account for smoothly integrated muscle activity was also functioning in the hypothalamus. Sherington proposed that in order for the extensor muscles of the extremities to function smoothly, the flexor muscles were "reciprocally inhibited." Gellhorn's conclusion was that in order for the sympathetic division to function in its normal physiologic state it had an inhibitory effect upon the parasympathetic division. This is the basis for his concept of hypothalamic "tuning."[13]

These studies can be integrated with the extensive studies of W. R. Hess which emphasize the ascending tracts to the cortex.[14] He called the responses associated with activation of the sympathetic division the "ergotropic"* responses. Those associated with the parasympathetic division he labeled the "trophotropic"* responses. Activation of the "ergotropic system" is associated with increased activity of the motor apparatus (skeletal and respiratory muscles). When the trophotropic system is "tuned up" and dominates activity, the parasympathetic discharges are quite apparent, along with a lessened activity and responsiveness of the somatic nervous system. Dr. Gellhorn's latest book, "Principles of Autonomic-Somatic Integrations"[14] provides a basis for the proposal of a "physiologic" brain model, which operates within the phylogenetic or "anatomic" model of MacLean. The "ergotropic" and "trophotropic" response systems quite obviously link the "three superimposed brains in the mind of man." Their influence on activating, inhibiting and coordinating activity in these three brains can provide the basis for reverberating circuits which will probably be the focus of study for neurophysiology in the last half of the 20th century.[15]

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*See Test Your Word Score Page 265.

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It's the Law

Hospital Liable for Unauthorized Autopsy

A man in a hospital expired because of lung cancer. A hospital resident requested the widow to sign a form authorizing autopsy. The form had already been signed by two witnesses. The widow refused permission for autopsy.

Through several mistaken impressions, an autopsy was performed. Ten days after death, the widow read the death certificate and discovered that an autopsy had been performed. A hospital official testified that the body had not been mutilated, nor the burial interfered with.

The widow testified that during his lifetime her husband had expressed objections to an autopsy. She stated that she had worried, lost sleep and weight, and had difficulty remaining at her work as the result of the autopsy.

Even though the body was not mutilated, or the burial interfered with, the widow's mental suffering was compensable, the Louisiana intermediary appellate court ruled. The award was $1500.*

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*Case Reference—French v. Ochsner Clinic, 200 So. 2d 371 (La., May 23, 1967; rehearing denied, July 5, 1967). The Citation—Vol. 16, No. 1, October 13, 1967.

Derivatively Speaking

Atheroma—from Greek *athere* (gruel) plus *oma* (swelling)

A Nawadir Anecdote

A very popular branch of literature, both in Arabic and Persian, was constituted by collections of strange and quaint anecdotes, called Nawadir. . . In such books a special section is often devoted to Medicine and Physicians.

One of the older Arabic books of this sort is a work entitled al-Faraj bada 'sh-Shidda ("Joy after Sorrow," or "Relief after Distress").

The case of a dropsical patient forms the subject of the fifth of these anecdotes. He was, after being dosed with various drugs, pronounced incurable by the physicians of Baghdad, and thereupon begged that he might be allowed to eat and drink what he pleased, and not, as he expressed it, be "destroyed by dieting." One day he saw a man selling cooked locusts, of which he bought and ate a large quantity. Violent purging followed this repast and lasted three days, at the end of which he was so weak that his life was despaired of, but he gradually recovered and was entirely cured of his dropsy. On the fifth day, being able to walk abroad, he met one of the physicians who had seen him before, and who was amazed at his recovery, about which he questioned him. "These were no ordinary locusts," said the physician, when he heard the story; "I should like you to point out to me the man who sold them to you." The seller being found and questioned, said that he collected the locusts in a village some miles from Baghdad, whither, for a small reward, he accompanied the physician, who found the locusts in a field in which grew quantities of the herb called Madharyun (Laurel-spurge or Spurge-flax), known to be beneficial in small doses for dropsy, but too dangerous to be commonly prescribed. The double coction which it had undergone in the locusts' bodies had, however, so mitigated its violence that its results had in this case proved wholly beneficial.

Other anecdotes in this book include a cure for apoplexy by flagellation, of pleurisy by a scorpion-bite, and of paralysis by a decoction of colocynth in milk.*

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*Edward G. Browne: Arabian Medicine, 1921.

On Sweats

Those sweats are the best in all acute diseases which occur on the critical days, and completely carry off the fever. Those are favorable, too, which taking place over the whole body, show that the man is bearing the disease better. But those that do not produce this effect are not beneficial. The worst are cold sweats, confined to the head, face, and neck; these in an acute fever pronosticate death, or in a milder one, a prolongation of the disease; and sweats which occur over the whole body, with the characters of those confined to the neck, are in like manner bad. Sweats attended with a miliary eruption, and taking place about the neck, are bad; sweats in the form of drops and of vapour are good. One ought to know the entire character of sweats, for some are connected with prostration of strength in the body, and some with intensity of the inflammation.*

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*From Hippocrates' Book of Prognostics

Some people are always grumbling because roses have thorns. I am thankful that thorns have roses.—Alphonse Karr

Pernicious Anemia in North American Indians

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RACE AND HEREDITY are major determining factors in acquiring Addisonian pernicious anemia. This disease occurs primarily in Caucasians residing in the temperate zone of North America and Europe or their offspring anywhere in the world. The predisposition or susceptibility is inherited probably as the effect of a single, dominant, autosomal‡ gene[1], and auto-immune phenomena have been implicated in the causation[2]. Familial incidence varies from 8 to 30%[3].

Pernicious anemia has been reported in most racial groups living in North America. It is more common in persons of Scandinavian, English, Irish and Canadian descent; relatively uncommon in those of Jewish, Russian, Greek, Italian, Scotch and German; and rare in pure-blooded Negroes and Orientals.[4] We have been unable to find any reported cases of pernicious anemia in persons of North American Indian descent. Two such cases in American Indians are reported in this paper.

Case Reports

Case 1

A 55-year-old male Indian from Ponsford, Minnesota, was referred to the Fargo Clinic on March 15, 1968, for evaluation of anemia. In November 1967, he noted the onset of burning of the tongue and loss of taste. He was hospitalized elsewhere from January 14 to 23, 1968, because of weakness. An upper G.I. series was done and he was transfused four units of whole blood. He was then dismissed from the hospital on a multivitamin preparation which he took daily until one week before being seen. In February 1968, he noted the gradual onset of numbness of the hands, legs and feet, rapidly progressing to unsteadiness of gait. He had lost 30 pounds in five months, despite a good appetite. He denied the use of alcohol, toxic exposure, diarrhea, icterus or melena. Chronic stasis and eczematoid dermatitis of the legs had been present for the preceding eight years. His hair had begun to turn grey at age 45 years.

He was a member of the Chippewa (Ojibway) tribe and resided on the White Earth Indian Reservation in West-Central Minnesota. Both his mother and his father were Chippewas from the same reservation. His father who had "Irish blood" died in 1930 at age 56 from anemia; his legs were previously "crippled." His mother who had "French-Canadian" blood had come originally from the Fort Francis, Ontario, area and had died at age 56 from heart trouble; she had no known anemia. A brother, 54, had anemia. No definite diagnosis was made.

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[†] Department of Neurology, The Neuropsychiatric Institute, Fargo, North Dakota.

[‡] See Test Your Word Score Page 265.

Physical Examination

Physical examination revealed a well-developed, grey-haired, stoic individual 69 inches tall, weighing 186 pounds (Figure 1). Blood pressure was 90/60 Hg.; pulse, temperature and respirations were normal. The tongue was red, smooth and deeply grooved. The legs showed chronic eczematoid dermatitis. Other positive findings were confined to the nervous system. Taste sensation was absent. Vibration sense was absent at the ankles and knees and slightly diminished at the wrists. Touch, pin-prick and two-point discrimination were symmetrically diminished in the upper and lower extremities distally in a stocking-glove distribution. All deep-tendon reflexes were absent. Babinski sign was absent. Moderate distal weakness was present in all extremities. His gait was ataxic and his Rhomberg's sign positive.

Laboratory Findings

Laboratory investigation revealed a hemoglobin of 10.6 gm. %, hematocrit of 32%, leukocyte count of 8050 per cmm. with a differential of 17% lymphocytes, 75% segmented neutrophils, 4% basophils and 4% eosinophils, and a sedimentation rate of 80 mm. per hour (Westergren). The platelet count was 164,000 per cmm. A peripheral blood smear showed occasional macrocytes and hypersegmented neutrophils, slight poikilocytosis and moderate anisocytosis. Gastric analysis showed a histamine-fast achlorhydria. A Schilling test using 0.5 microcuries of Racobalamin 57 revealed 1% urinary excretion in 24 hours before and 4.5% excretion after intrinsic factor. A stool examination was guaiac negative and also negative for ova and parasites, fat and meat fibers. Serum protein electrophoresis revealed a slight elevation of gamma globulin at 1.96 gm. %. The following tests were normal or negative: V.D.R.L. flocculation test, routine urinalysis, serum iron, fasting blood sugar, blood urea nitrogen, serum cholesterol, bromsulfthalein dye excretion, urine for porphobilinogen and serum carotene. Chest x-ray revealed a prominent vascular shadow at the left hilus and minimal pleural thickening at the left apex. X-ray of the esophagus, stomach and duodenum was negative. A 12-lead electrocardiogram was normal. His blood type was Group A, Rh positive (D).

Because of the severe peripheral neuritis, he was hospitalized for two weeks and received vitamin B-12, 1000 micrograms, intramuscularly, daily. After one week of treatment, his taste returned. However, the numbness of the extremities, the absent reflexes, and the broad-based gait persisted. On March 29, 1968, the hemoglobin was 12 gm. %, sedimentation rate 54 mm. per hour (Westergren) and the reticulocyte count 3.3%.

He was dismissed from the hospital and advised to receive vitamin B-12, 1000 micrograms, intramuscularly twice weekly during the month of April.

When seen on May 7, 1968, his gait had improved considerably, but the numbness in the hands and feet persisted. He had gained eight pounds. He was still areflexic and had sensory deficits in the extremities. The hemoglobin was now 13.8 gm. % and he was advised to receive vitamin B-12, 1000 mcg., intramuscularly every three weeks.

Case 2

A 65-year-old male Indian from Mandaree, North Dakota, was referred to the Neuropsychiatric Institute Hospital in Fargo on March 7, 1967, for evaluation of numbness and burning dysesthesias of the upper and lower extremities of three months' duration. The dysesthesias originated in the fingers and then the toes. He had also noticed a shock-like sensation radiating from the neck to the shoulders, arms and down the back with neck flexion (Lhermitte's sign). Cervical spine traction had been attempted elsewhere one month prior to admission without benefit. The numbness and burning subsequently progressed, ascending to the wrists and knees. His voice had been raspy for one month and he had lost eight pounds in the preceding three months. He denied alcohol abuse, toxic exposures, previous anemia or diabetes and was taking no medications.

He was a member of the Hidatsa (Gros Ventre) tribe and resided on the Fort Berthold Indian Reservation in West-Central North Dakota. There was no family history of anemia. He thought that he was pure-blooded although he recalled that his maternal grandmother had light skin and brown hair.

Physical Examination

Physical examination revealed a well-developed, well-nourished, healthy-appearing individual. His height was 69 inches and weight 174 pounds. Blood pressure was 142 systolic and 90 diastolic; pulse, temperature and respirations were normal. The tongue appeared normal. Neck flexion produced a shock-like sensation radiating down both arms. Foraminal compression signs were absent. Muscle strength was normal in the upper and lower extremities. The deep tendon reflexes were active, equal and normal in the upper extremities. The knee and ankle jerks were slightly hyperactive. Babinski sign was absent and there was no clonus. Sensory examination including touch, pinprick, two-point discrimination, vibratory and position senses were normal. The gait was normal and Rhomberg's sign was negative. Indirect laryngoscopy revealed normally functioning vocal cords. The remainder of the physical examination was not remarkable.

Laboratory Findings

Laboratory investigation revealed a hemoglobin of 11.2 gm. %, hematocrit of 33%, leukocyte count of 7500 per cmm. with a differential of 25% lymphocytes, 66% segmented neutrophils, 3% monocytes and 6% eosinophils and a sedimentation rate of 50 mm. per hour (Westergren). The reticulocyte count was 2.7%. A peripheral blood smear showed many macrocytes, marked anisocytosis and poikilocytosis, occasional nucleated red blood cells and some hypersegmented polymorphonuclear cells with up to seven lobes. First-strength purified protein derivative and histoplasmin skin tests were both positive (2+). Blastomycin and coccidioidin skin tests were negative. A Schilling test using 0.5 microcuries of Racobalamin 57 revealed 2.3% urinary excretion in 24 hours before and 12.5% excretion after intrinsic factor. The following laboratory tests were normal or negative: V.D.R.L. flocculation test, routine urinalysis, fasting blood sugar, blood urea nitrogen, serum calcium, serum acid and alkaline phosphatase, and serum transaminase. Chest x-ray revealed a 3-cm. density in the postero-inferior aspect of the right hilus and a few calcific foci at the left hilus and left base. Tomograms revealed that the right hilar mass was sharply outlined and contained calcium. Skull x-ray was negative. X-ray of the cervical spine revealed narrowed disc spaces throughout and lipping of the anterior and posterior aspects of C-3 through to C-7. X-ray of the esophagus, stomach and duodenum revealed large, irregular calcific densities in the left mid-abdomen representing calcification in lymph nodes; there was also a small, self-reducing hiatal hernia and a normal small bowel pattern.

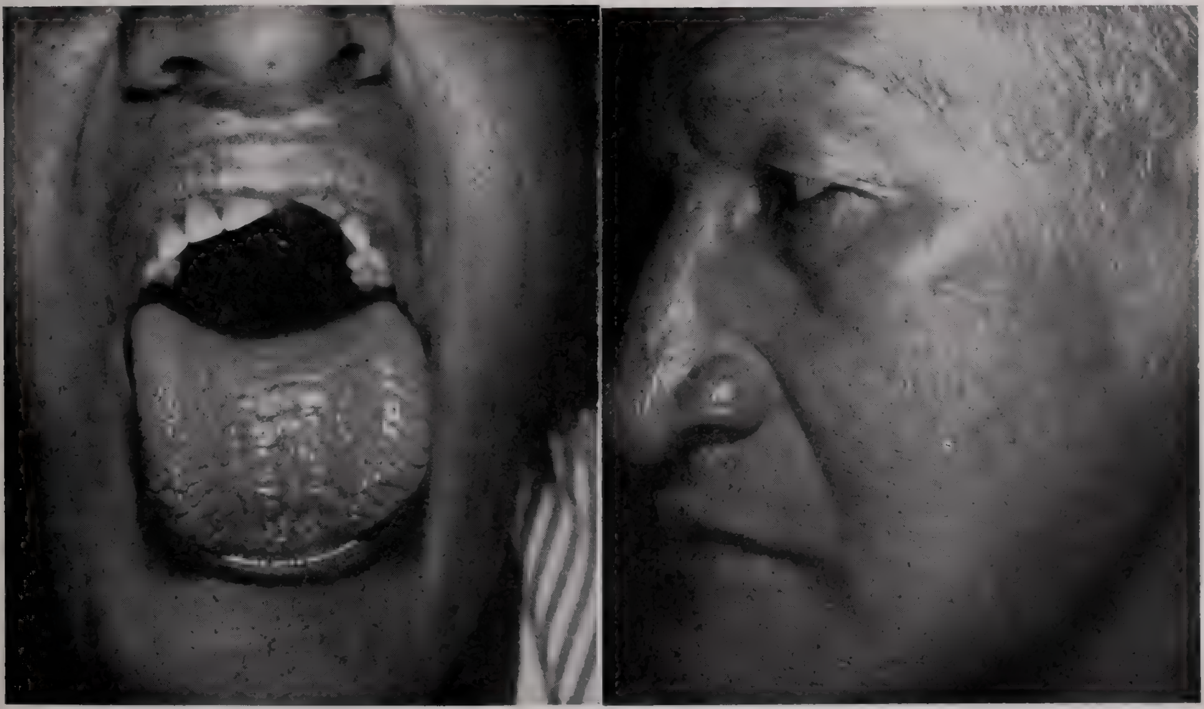
The patient was given vitamin B-12, 1000 micrograms intramuscularly daily, for one week. He was dismissed from the hospital on March 16, 1967, to be followed by his local physician who was advised to give him vitamin B-12 1000 micrograms intramuscularly every other day for two weeks, then weekly for three weeks and then once monthly.

Follow-up with his local physician on March 26, 1968, revealed that the hemoglobin was normal; but the numbness and burning dysesthesias of the hands and feet had persisted.

Comments

The North American Indian probably originated from Northeastern Asia, having crossed the Bering Strait to the Western Hemisphere approximately 15,000 years ago.[5] The earliest groups of hunters settled in Alaska, the Yukon and the Northwest Territories as ancestors of the present day Eskimos. Some migrated further south to inhabit Canada, the United States, Mexico, Central and South America as Indians. Radiocarbon dates indicate that men had reached the tip of South America some 8,000 years ago. The term Indian was first used by Columbus to describe the natives of the New World that he believed to be Indios (natives of India). There is some question whether more Indians exist now than when Columbus discovered America. At present, about 500,000 Indians live in the United States and are confined largely to 150 to 200 usually squalid reservations. Full-blooded Indians are rare.

The main health problems of the Indian population are infant mortality, malnutrition, mental retardation, cirrhosis of the liver, violent injuries and infections. Contact with Caucasians has subjected the Indians to tuberculosis and venereal diseases; also through intermarriage they have become subjected to diseases with a genetic predisposition, such as pernicious anemia. This has been true also



Figure—Case 1 showing smooth, shiny tongue of pernicious anemia.

of the American Negro; for pernicious anemia, although rare, does occur, probably as a result of intermarriage. Of 329 cases of pernicious anemia seen at Johns Hopkins University between 1925 and 1940 where the white:colored ratio was 3:1, there were 33 cases in Negroes.[6] At Cook County General Hospital, pernicious anemia occurred in 36 Negroes and 170 Caucasians per 100,000 hospital admissions.[7] Pernicious anemia is rare in full-blooded Orientals,[8] of whom the North American Indian is likely a descendant.

Of 85,300 discharges from Public Health Service Indian and community hospitals in 1967, there were 29 cases with a primary diagnosis of pernicious anemia and other macrocytic anemias; their data does not separate the two varieties. The number of cases may be smaller than 29 since some patients may have been admitted more than once during the year.[9]

The Director of Indian and Northern Health Services of Canada has informed us that pernicious anemia is not one of the diseases cross-indexed in Ottawa from the hospital records of Indians and Eskimos. The Charles Camsell Hospital, Edmonton, Alberta, the main referral center for Alberta Indians and the Eskimos and Indians of the Northwest and the Yukon Territories, a population of 35,000 Indians and 5,000 West Arctic Eskimos, had no Eskimos with a diagnosis of pernicious anemia in the past 15 years. However, five male and two female Indians had the diagnosis recorded. All but one were Alberta Indians and most were of mixed blood with White French-Canadian, or *métis** admixture. The diagnosis was not proven in approximately half of the patients. All five males were 57 years of age or older; one female was 38 and the other 81 years old. One laboratory-proven case of pernicious anemia occurred in a 75-year-old Prairie-Cree Indian who considered himself pure-blooded and looked so.

Summary

Two cases of Addisonian pernicious anemia in North American Indians of mixed-blood are presented. Both patients were afflicted more neurologically than hematologically. Pernicious anemia is uncommon in full-blooded Indians and the genetic predisposition has probably come through intermarriage with Caucasians. It is recommended that pernicious anemia be considered in Indians with neurological manifestations or anemia.

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*See Test Your Word Score Page 265.

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Your Chances Are Good

You have two chances—one of getting the germ and one of not. And if you get the germ you have two chances—one of getting the disease and one of not. And if you get the disease you have two chances—one of dying and one of not. And if you die—well, you still have two chances.—Author unidentified

When man is no longer anxious to do better than well, he is done for.—Haydon

Acute Neurological Deterioration Following Lumbar Puncture

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In 1934 WALTER DANDY began a discussion on the use of lumbar spinal puncture by stating: "Lumbar puncture is one of the most used and abused procedures employed for neurological diagnosis and therapy." Later in the same discussion he said: "I have seen at least twenty deaths resulting from lumbar puncture." In this same report he modified this statement by saying he had reference only to cases in which increased intracranial pressure was suspected or found to be present.[1] The dangers inherent in this procedure done under these circumstances have subsequently been abundantly documented by other neurosurgeons. Frankel and German reported a two-per-cent mortality in patients with brain tumors, and others have had a similar experience.[3] In spite of these formidable figures there has been an increasing tendency to minimize the dangers of lumbar puncture, especially by those not so intimately responsible for patients with elevated intracranial pressure.[2]

Because neurosurgeons do have this intimate responsibility, besides almost daily experience with this problem, they have become concerned over these trends. In order to emphasize this concern the following report of six cases which came to the attention of the Neurosurgical Service at the University of Minnesota in a single six-month period from August 1, 1967, through February 1, 1968, are presented. In all the patients the neurological deterioration seemed unequivocally related to the lumbar puncture. Additional cases in which less catastrophic changes occurred have been omitted, and patients with spinal cord tumors with increased neurological deficit after myelography or spinal puncture are also not included.

Case Reports

Case 1

A 46-year-old lady with a two-week history of occasional headaches, increased fatigue and some mental deter-

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ioration was admitted to a hospital and a diagnosis made of psychological depression. Psychiatric consultation suggested the depression was on an organic basis. Skull roentgenograms and an electroencephalogram revealed no abnormality. The lumbar spinal fluid pressure was measured at 280 mm. of water. The morning following the lumbar puncture the patient was found to be comatose, but the exact duration of this state could not be definitely determined.

Examination after transfer to the University Hospitals on August 1, 1967, revealed the patient to be comatose and unresponsive to pain. There was severe bilateral papilledema and a left abducens nerve paresis. The deep tendon reflexes were hyperactive in the lower extremities, and the Babinski response was positive bilaterally with bilateral ankle clonus. The clinical impression was that the patient had a right frontal lobe neoplasm with herniation of the temporal lobe into the incisura of the tentorium secondary to increased intracranial pressure. A right carotid angiogram substantiated the diagnosis. Emergency craniotomy and right frontal lobectomy were performed with removal of a glioblastoma multiforme.

Postoperatively the patient made a dramatic recovery and 11 days later the patient's family considered her quite normal except for a mild change in her mental status. She was transferred to a convalescent hospital for a combination of radiation therapy and chemotherapy.

Case 2

A two-and-one-half-year-old boy was well until August 1967, when there was the onset of episodic vomiting and a minor personality change. Gradually he became progressively more withdrawn and more dependent and began to sleep for longer periods of time. On October 14, 1967, the patient fell down a flight of stairs and thereafter limped, favoring his right leg. On October 19, 1967, the vomiting became projectile and he staggered when he tried to walk. Because of increasing lethargy he was hospitalized that night. About 2:00 a.m. the patient had an episode described as a seizure. He then had a lumbar puncture which revealed grossly bloody fluid. This procedure was followed by a steadily increasing number of extensor spasms. When the patient arrived in the emergency room of the University Hospitals he was opisthotonic and responded to stimulation by decerebrate posturing. Neurological examination revealed the child to be comatose with a decerebrate response to pain. He had very hyperactive deep tendon reflexes, bilaterally positive Babinski signs and severe bilateral papilledema. A tentative diagnosis of posterior fossa neoplasm was made. An emergency ventriculogram showed obstruction of the aqueduct, and immediately thereafter a craniotomy revealed a medulloblastoma involving the vermis. Within the neoplasm was a large hematoma. All the grossly visible neoplasm was removed. Postoperatively the patient recovered from his decerebrate state, and his subsequent course was one of gradual improvement. He was given deep roentgen therapy to the posterior fossa and spinal axis. At the time of discharge he was alert but had a residual right hemiparesis and diminished visual acuity.

Case 3

A 73-year-old man, partially crippled with rheumatoid arthritis, had a three-week history of dizziness, suboccipital headaches, staggering gait and double vision. The day before admission he vomited four times and that evening became mentally confused. Examination revealed an obtunded patient who responded only with grunts. Funduscopic examination showed optic discs with sharp margins. Carotid pulses were equal and there were no bruits. The patient had a right hyperreflexia and a positive left Babinski sign. He could not look to the left nor upward. The initial diagnostic impressions were stroke syndrome or intracranial tumor. Immediately after admission a lumbar puncture was performed. The fluid was clear, questionably yellow-tinged, and the pressure was 230 mm. of water. The following morning the patient was comatose. An electroencephalogram was performed which revealed a focal delta area in the right frontal region. At this point neurosurgical consultation was obtained and a tentative diagnosis of posterior fossa tumor was made. Shortly thereafter ventriculography showed evidence of a mass in the cerebellum. A posterior fossa exploration revealed a large metastatic tumor in the left cerebellar hemisphere. The neoplasm was removed without difficulty but the patient did not recover and expired two days after operation.

Case 4

A 26-year-old man developed severe bifrontal headache about two weeks prior to admission. He was treated for sinusitis for a week without relief. He then developed a temperature elevation, was found to have a bacterial tonsillitis, and was treated with intramuscular penicillin. Twelve hours later he suddenly developed left leg numbness and weakness. The following day he had a severe hemiparesis and nuchal rigidity. Penicillin therapy was continued for two more days. Then a lumbar puncture was performed. Four hours later he developed generalized seizures and became unresponsive with fixed, dilated pupils.

He was transferred to the University Hospitals as an emergency case. Examination at the time of admission revealed a very lethargic, unresponsive patient whose pupils were equal and reacted slowly to light. There was a severe left hemiparesis. There was no papilledema. Skull films revealed the presence of a frontal sinusitis. Brain scan and carotid angiogram were within normal limits. A diagnosis of cortical thrombophlebitis was made and the patient successfully treated with intravenous antibiotics and anticonvulsants after the right frontal sinus was drained surgically. He was discharged from the hospital on the eleventh postoperative day without a neurological deficit.

Case 5

An 11-month-old girl had developed focal seizures one month prior to admission. These involved the left side of the face and had followed a bout of left otitis media. She had been treated with penicillin and sulfadiazine. An electroencephalogram revealed no abnormality. The seizures were controlled with phenobarbital, mebaral, and mysoline. Three days prior to admission the child had begun to vomit and was found to be very lethargic. On the morning of admission a lumbar spinal puncture was performed. The pressure was not measured but was "believed to be elevated." There were no cells; the protein content was 28 mgm. per cent. Shortly after the lumbar puncture the patient became comatose with fixed, dilated pupils. She was immediately transferred to the University Hospitals.

At the time of admission the patient was totally unresponsive with a left-sided flaccid paralysis. The pupils were dilated and fixed and there was evidence of bilateral papilledema. Ventricular needles were placed into both frontal horns in the emergency room and purulent material obtained bilaterally. An emergency brain scan demonstrated a large right posterior-frontal mass. It was believed that a large brain abscess had ruptured into the ventricular system or that the patient had a purulent encephalitis. Treatment with intravenous antibiotics was instituted but the patient continued to deteriorate and died on the third day after admission. Postmortem examination revealed a diffuse encephalitis. The etiology was not proven.

Case 6

A 21-year-old male gave a history of headaches, nausea, and personality change of one year's duration. Examination upon admission revealed ataxia, right-sided cerebellar signs, nystagmus, but no papilledema. A diagnosis of posterior fossa tumor was made, but later revised when a right parietal focus was found on brain scan. Carotid angiography was normal. A combined pantopaque-air ventriculogram was performed via the frontal approach, but visualization of the right lateral ventricle and posterior fossa was inadequate. Without papilledema and with access to the ventricle above, a pneumoencephalogram was deemed safe. An 18-spinal needle was introduced at the fourth lumbar level; no fluid was removed; 7 cc. of air were slowly injected. The patient immediately became decerebrate. He was returned to the supine position and recovered spontaneously in a few seconds. No further air was injected. Because of the positive brain scan and failure to fill the lateral ventricle with air, a presumptive diagnosis of a deep right parietal tumor was made. An emergency craniotomy revealed a large thalamic glioblastoma nearly filling the lateral ventricle as well as obliterating the posterior part of the third ventricle and upper aqueduct. The intraventricular portion of the tumor was removed and a ventriculo-cisterna magna shunt performed. The patient recovered well initially but deteriorated after several months and expired with brain stem infiltration by the tumor.

Discussion

The mechanisms by which catastrophic events associated with lumbar puncture occur have been debated at length. It is now generally agreed that a shift of intracranial contents with internal herniation of brain substance is the primary pathogenetic mechanism. These herniations may take several forms, the most important of which are herniation of the medial aspect of the temporal lobe (hippocampal gyrus or uncus) through the tentorial opening on one or both sides, and thrusting of the cerebellar tonsils through the foramen magnum.[1]

Uncal Herniation

Herniation of a temporal lobe is usually accompanied by ipsilateral compression of the third cranial nerve with resultant pupillary dilatation and contralateral body paralysis due to compression of the cerebral peduncle. Occasionally the opposite peduncle may be compressed against the tentorial edge, resulting in a "falsely" localizing ipsilateral hemiparesis. In this type of herniation death usually results from mid-brain hemorrhages secondary to vascular damage.

Tonsillar Herniation

The pressure cone formed by herniation of the cerebellar tonsils through the foramen magnum is also well known. Symptoms arise by compression of the medulla and upper cervical cord. Early cases may present bilateral spasticity, hyperreflexia, positive Babinski signs, intermittent decerebration and hiccoughing. Death occurs as a result of medullary failure, usually cessation of respiration.

Other Incisural Herniations

Less well known internal herniations also occur. The supracallosal gyrus may herniate laterally beneath the falx of the cerebrum. The cerebellum may herniate upwards to occlude the posterior cerebral arteries, producing "cortical" blindness due to infarction of the occipital lobes, either uni- or bilaterally. This upward displacement of the cerebellum may compress the upper midbrain, mimicking a pineal neoplasm. Rarely the brain may herniate into the pituitary fossa creating an acute hypopituitarism.

Indications

This presentation should not be construed as condemning the judicious use of lumbar puncture. Certainly the procedure is an invaluable diagnostic and therapeutic aid in many situations. Even increased intracranial pressure alone is not a contraindication, for pressure elevations are commonly found in meningitis, subarachnoid hemorrhage, and pseudotumor cerebri where spinal tap is rarely attended by any difficulty. It is primarily in the presence of an *intracranial mass lesion,* especially one located in the posterior fossa, that lumbar puncture becomes a dangerous procedure. When there is a strong clinical suspicion that a space-occupying lesion exists, lumbar puncture is usually ill-advised. Only in very special situations, e.g., a suspected acoustic nerve tumor, do a lumbar puncture and spinal fluid examination serve any useful purpose in the diagnosis of brain tumors. When clinical suspicion is high, there is nothing that can be learned from lumbar puncture which will change the course of the evaluation.

By competent neurological evaluation and funduscopic examination, the presence of increased intracranial pressure can be adequately assessed without the risk of herniation that exists if this elevation is determined by spinal tap. When signs and symptoms strongly suggest a tumor, certainly no cytologic or chemical finding in the spinal fluid will alter the necessity of studying the patient with roentgenograms, radioactive isotope brain scan, angiography, or air encephalography as indicated. It is true that examination of the spinal fluid would eliminate the possibility of meningitis, encephalitis or subarachnoid hemorrhage, but the clinical differentiation of these from brain tumor should rarely be a problem; so this is not really a practical consideration.

Necessity

It is believed that before a lumbar puncture is performed, it is well to consider carefully what combination of data may be obtained. These data refer, of course, to cerebrospinal fluid dynamics, chemical analysis, and cytological examinations. If this information, whatever it may be, will not influence the subsequent management of the patient, it is safe to say that the contemplated spinal puncture is unnecessary. Furthermore, in addition to the mortality and morbidity that may arise as a result of the puncture, an untimely spinal tap may render subsequent diagnostic procedures, such as a pneumoencephalogram or myelogram with cerebrospinal fluid analysis, much more difficult to execute and evaluate. This frequently will mean an unnecessarily prolonged hospitalization for the patient.

Hazards

It has often been said that an atraumatic tap with a small needle and removal of a small amount of fluid is a safe procedure. While it certainly is desirable to perform the puncture as atraumatically as possible, it is not likely that either of these precautions adds great safety in the presence of a brain tumor. With increased pressure the initial amount of fluid removed is not nearly so important as that which leaks through the dural hole afterwards. It has been our experience that patients having a laminectomy 24 hours following myelography often have extradural cerebrospinal fluid and a visible hole in the dura through which cerebrospinal fluid can be seen to flow.

Summary

We have reported six cases in which profound neurological deterioration occurred in direct consequence of lumbar puncture or air encephalography. These were collected at random in a single six-month period from patients seen by the neurosurgical service of the University of Minnesota Hospitals and are reported to emphasize the dangers of lumbar tap when a space-occupying intracranial mass is present. It is our general contention that lumbar puncture is superfluous in the diagnosis of brain tumor and that *safe* punctures cannot be performed with certainty. All patients to undergo diagnostic or therapeutic spinal tap should be carefully evaluated for signs and symptoms of increased intracranial pressure, and should have a funduscopic examination to determine the presence or absence of papilledema. If such signs and symptoms exist we believe lumbar puncture presents an appreciable danger and should be avoided.

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Grinszpan, Goldstein and Divito[2] used Lomotil in 20 children with diarrhea and also reported a prompt disappearance of diarrhea. Harris and Beveridge[3] in a double-blind study of 50 children with diarrhea, however, found no clear pattern to suggest that Lomotil influenced the course of the condition.

Michener, Brown and Turnbull[4] added evidence supporting the beneficial effects of Lomotil in 80 children, concluding that Lomotil was highly useful in controlling abdominal cramping, diarrhea and hypermotility.

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8-12 yr.	1 tsp. 5 times daily (10 mg.)
Adults:	2 tsp. 5 times daily (20 mg.) or 2 tablets q.i.d.

Based on 4 cc. per teaspoonful.

Maintenance dosage may be as low as one-fourth the initial daily dosage.

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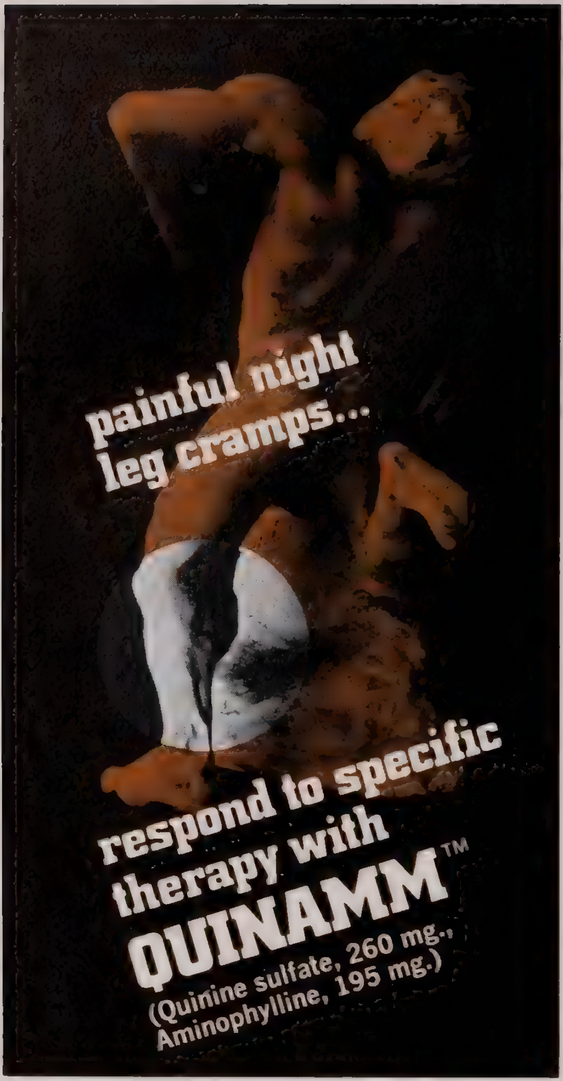

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Editorials

Adenomammectomy*

ADENOMAMMECTOMY as a more complete type of procedure for obtaining breast biopsy specimens would seem to be more radical than would be necessary in most circumstances. It is true that even with our more sophisticated methods of supplementing physical examination in the evaluation of breast lesions, there continue to be a number of patients who require operative approaches for the final and complete reassurance of both the physician and the patient. Limited biopsy specimens from indeterminate nodules through minimal incisions have sometimes led to overlooking an adjacent more significant nodule than the one that seemed apparent to the surgeon through this limited approach. This, however, is uncommon and related directly to the responsibility of the individual surgeon. It would not appear to be justification for a radical type of local excision of the breast for every indeterminate lesion.

The surgeon should have a strong responsibility to obtain an excellent cosmetic result whenever possible with breast surgery. Usually he can accomplish this by judiciously limiting the excision of breast tissue. The use of a circumareolar incision to obtain biopsy specimens in all quadrants of the breast is usually possible and permits a satisfactory cosmetic result with respect to the resulting scar. For that rather uncommon group of patients who have sufficient fibrous or cystic mastitis, with or without pain, in whom excision of extensive portions of the breast would seem indicated and who may have had multiple biopsy specimens taken previously, it would seem more reasonable at this time to be thinking of a complete subcutaneous mastectomy, with replacement by a suitable prosthesis. Adenomammectomy and attempted reconstruction of the breast obviously leave considerable breast tissue behind as a threat for neoplasia in the future.

The final word on breast prostheses is a long way from being written, but it would seem reasonable to use those techniques that are available at the present time when one is dealing with benign disease and contemplating the sacrifice of a major amount or all of the breast to gain reassurance and relief of pain. Even with certain malignant lesions, the survival of patients may be such that the use of subcutaneous prostheses will have an increasing role.

Philip E. Bernatz, M.D.
Rochester, Minnesota

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*Rice, Carl O.: Adenomammectomy: Origin and Technique. Minnesota Med. 51:1325, 1968.

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John F. Kennedy, Inaugural Address

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Embolism

Clinicians are all familiar with thromboembolic diseases, but the less common varieties of embolic phenomena are not as well known. Evarts'[1] discussion of fat embolism should stimulate interest in this syndrome, particularly in those who deal with traumatic injuries.

A multitude of substances, both endogenous and exogenous, have gained access to the circulation, sometimes by iatrogenic means.

Recent studies have emphasized the importance of atheromatous embolism. Fragments of atheromatous material, chiefly cholersterol crystals derived from plaques in large arteries, may occlude smaller vessels. This disease may imitate a variety of conditions, including polyarteritis nodosa, peripheral vascular disease, and subacute bacterial endocarditis[2]. Muscle biopsy has been useful in establishing the diagnosis, also direct visualization of retinal emboli.

Some examples of exogenous emboli are: (1) fragments of indwelling venous catheters sheared off by the needle tip[3]; (2) the ball from an intracardiac ball valve prosthesis[4] (decrease in size over a period of time may allow the ball to escape from its cage with predictably catastrophic results); and (3) the tip of a varicose vein "stripper[5]."

Improvements in design and use of these materials should decrease the incidence of exogenous embolism, but those familiar with Murphy's Law* will realize that episodes of this nature will continue to occur.

David A. Berman, M.D.
Minneapolis, Minnesota

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*Murphy's Law—Anything that can possibly go wrong, sooner or later will go wrong.

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Food Allergy and Gastrointestinal Allergy*

Many patients with obvious allergy to food do not consult a physician because it is apparent to them that if they avoid the easily identified offending food, they will not have allergic symptoms. Strawberries, seafood, fish, and nuts commonly cause acute and often transient symptoms. The importance of foods causing persistent allergic symptoms is, however, a controversial matter. Some allergists find that foods frequently cause chronic nasal symptoms and asthma. Many other allergists are unable to confirm these observations. The importance of making this diagnosis is apparent, since removal of the offending foods should cause a disappearance of symptoms. Diagnostic tests, in general, are on a shaky scientific foundation. Skin testing for offending foods has been found to be generally unreliable. Elimination diets are sometimes helpful. A carefully taken clinical history is certainly important, but patients often are uncertain as to the importance of various foods. A provocative diet containing the suspected food given on several separate occasions may be a valuable technique. Another type of testing involves the leukopenic index, which is based on the unproved idea that leukopenia occurs after the ingestion of a food to which a patient is allergic.

The provocative intradermal food test has been proposed as another diagnostic procedure. This involves attempting to induce al-

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*Johnson, K. J.: Critique of the Provocative Intradermal Food Test. Minnesota Med 51:195, 1968.

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lergic symptoms by intradermal injection of relatively concentrated food extracts. If a reaction occurs, a further intradermal injection of the same extract in higher dilution is given to relieve the provoked symptoms. The mechanism involved in relieving symptoms by further injection of the same material in a diluted form is not clear, and the validity of this type of testing awaits double-blind studies.

Gastrointestinal allergy is a term describing symptoms involving the gastrointestinal tract caused by allergic (antigen-antibody) reactions. Usually foods are implicated, but drugs, injectants, and inhalants also are believed to produce gastrointestinal allergy. Possible symptoms cover a wide spectrum of gastrointestinal complaints and none are specific. Ingelfinger and co-workers[1] have proposed three criteria for diagnosis. 1. The symptoms should be caused by substances that are innocuous when given to the bulk of the population. 2. Lesions or functional changes in the gut should be demonstrated. 3. Emotional and mechanical factors should be excluded and the role of subjective attitudes minimized by testing various substances under carefully controlled conditions. The offending food, which is given in a double-blind fashion, should cause reproducible symptoms, signs, or x-ray findings at a rather constant interval; and other foods should not do this.

Many disorders are associated with excessive loss of proteins from the gastrointestinal tract. Waldmann and associates[2] studied six children who had a syndrome consisting of edema, anemia, hypoalbuminemia, hypogammaglobulinemia, eosinophilia, and growth retardation. There was a significant amelioration of the clinical symptoms and disorders of protein metabolism in three of these patients when a milk-free diet was given. When milk was re-introduced into the diet, there was diarrhea and vomiting, increased eosinophilia, an increase in the number of Charcot-Leyden crystals in the stools, and a worsening of the protein-losing gastroenteropathy. They called this syndrome "allergic gastroenteropathy."

Greenberger and colleagues[3] have reported protein-losing enteropathy associated with gastrointestinal allergy in an adult. A specific food intolerance was correlated with the symptoms of gastrointestinal involvement and changes in the intestinal mucosa, including an increased infiltration of eosinophils. An exhaustive work-up failed to reveal any other cause for the patients' protein-losing enteropathy, and it was proposed that the excessive enteric loss of protein was due to injury to the gastrointestinal mucosa by specific food allergens. The mechanism of this loss in patients with gastrointestinal allergy has not been defined. It may be due to a localized hypersensitivity reaction in the intestinal mucosa with development of mucosal edema and passive diffusion of plasma proteins into the intestinal lumen. Such a process could conceivably subside rapidly when the offending agent is removed from the intestinal tract.

Gastrointestinal allergy must be differentiated from almost all other organic diseases of the gastrointestinal tract. This diagnosis can be made only when other pathologic conditions have been carefully excluded.

Harry A. Swedlund, M.D.
Rochester, Minnesota

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The surgeon knows everything and does everything. The internist knows everything and doesn't do anything. The psychiatrist doesn't know anything and doesn't do anything.—Author unknown

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He who sits with his back to a draft sits with his face to a coffin.—Spanish proverb

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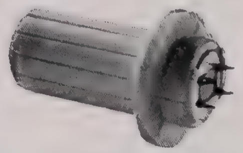

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Open Heart Surgery in Elderly Patients

THE PRACTICING PHYSICIAN in the community hospital has to be a realist. New procedures, often glamorized both in medical publications and by the lay press, must be given a hard look; for, if results and mortality rates do not measure up to expectations, then the local medical doctor must bear much of the burden of the poor result and, unlike the relatively sequestered specialist, must live with the family.

Open heart surgery a decade ago was a high-risk procedure and failures were not uncommon; hence a skeptical attitude by the general physician to this innovation was not without justification. Yet when the procedure was successful, the result was often startling, for the correction of a defective valve or the closure of a septal defect can turn a pitiful cardiac cripple into a robust human. While techniques were being refined, open cardiac surgery was limited largely to correction of congenital defects, for only in the very young did the great potential benefit warrant the high risk of the operation.

Times have changed and open heart surgery is no longer an innovation; it has withstood the test of time and is an accepted procedure. The adult with acquired valvular disease that limits his capabilities and restricts his activities should be considered for corrective surgery. Accurate preoperative assessment, technical operative finesse, proficiency in the bypass, and diligent postoperative care have lowered the risk sufficiently so that the realistic clinician must now reassess his attitude toward surgery for his patient.

It seems to this viewer that now instead of asking: why should the patient be subjected to the risk of surgery, one should ask: why shouldn't the patient be offered the benefits of surgical correction. The four remarkable patients with an average age of 75, who successfully underwent open heart surgery, as reported here by Doctors Kiser, Peterson, and Johnson*, amply demonstrate the rewards of this change of attitude.

Harrison H. Farley, M.D.
Minneapolis, Minnesota

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*See page 231.

Vertebral Basilar Artery Insufficiency

THE EXCELLENT ARTICLE by Dr. Klassen in the September issue* comprehensively covers this subject in its various aspects. A pure hemiplegia may be either cerebral or pontine. A lesion of the pons may produce a complete hemiplegia similar to that of a lesion in the motor cortex or the internal capsule of the cerebrum. To localize such a brain stem or posterior fossa involvement, one must rely on a Horner's syndrome, vestibular manifestations, cerebellar symptoms, cranial nerve findings, and various visual manifestations. The latter occur because the posterior cerebral arteries supply the visual area and originate from the basilar artery. In hemi-sensory involvement of deep sensation, such as position sense, vibration sense, and stereognosis, the lesion is usually cortical or supratentorial; whereas, when pain and temperature are involved alone, the brain stem is more apt to be involved.

Generally, most cases are in the arteriosclerotic age group, and arterial insufficiency of the vertebral basilar circulation is readily suspected. A man in his early forties complained of shifting hemi-sensory symptoms. Neurological evaluation was repeatedly negative; therefore conversion hysteria or psychoneurosis was suspected. He had been demoted several times in his job and was the

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*Klassen, A. C.: Vertebral-Basilar Insufficiency. Minnesota Med 51:1183, 1968.

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only unsuccessful sibling in his family. He finally developed a quadriplegia and definite bulbar symptoms. Autopsy showed a marked stenosis of the basilar artery (without thrombosis) resulting in demyelinization of both pyramidal tracts in the pons.

Difficulty in the differential diagnosis is demonstrated by the following care and conditions. An older patient with some evidence of arteriosclerosis had two episodes of transitory squint and diplopia with some vague cerebellar findings. At autopsy this proved to be two aneurysms of one vertebral artery and calcification of the dentate nuclei of the cerebellum. Vertebral basilar disease occasionally may mimic multiple sclerosis with fluctuating cerebellar findings, cranial nerve findings, and pyramidal tract and sensory findings. The age of onset generally makes the differential not too difficult. The so-called hemiplegic variety of migraine will produce transitory hemisensory and hemiplegic symptoms. Occasionally these may remain permanent. The posterior circulation, though rare, may be involved in migraine, producing various combinations of a cerebellar and brain stem involvement. The age of onset and a positive family history generally point to a correct diagnosis.

A man in his early sixties with some evidence of arteriosclerosis and elevated blood pressure, in whom the diagnosis of vertebral basilar artery insufficiency seemed apparent, proved to have an angioblastoma. Its removal resulted in complete cure of the patient.

Another patient had episodes of diplopia and also separate episodes of vertigo. He was first treated for Meniere's disease. When the transitory episodes of diplopia occurred, the patient was referred for neurological study. He was negative neurologically, but vertebral angiography showed a complete occlusion of one vertebral artery in the vertebral canal in the cervical region. The other artery was small. At operation an osteophyte was found obstructing the artery. This was removed and the patient has remained free of symptoms now for a number of years.

Dr. Klassen suggests that angiography should be reserved mainly for cases showing a suspected subclavian steal. A significant difference in blood pressure in the arms and symptoms following exercise of the arms leads one to suspect this condition. Unfortunately some cases of subclavian steal do not show such a difference in blood pressure.

In our experience vertebral angiography by catheterization of the brachial artery is free of serious complication. As far as I know, no extensive autopsy study of the extracranial vertebral arteries has been performed. Perhaps more angiography followed by more autopsy studies would help improve our diagnostic and therapeutic skill. As yet no one knows precisely which cases should have contrast studies.

In a number of studies anticoagulation therapy has seemed to be of definite value, but in a few the outlook seems little different with or without such treatment. A fair percentage of cases of infarction of the brain stem have been preceded by intermittent insufficiency. Actual infarction of the brain stem is frequently fatal or leaves the patient with serious residuals. Until we are able to predict which cases of intermittent insufficiency will go to infarction, there remains a strong argument in favor of anticoagulation therapy.

Harold H. Noran, M.D.
Minneapolis, Minnesota

Bad Temper

As a youngster I once happened to see a man opening a door in a hurry, and when things did not go as he wished, he bit the lock, kicked the door, and reviled the gods; his eyes became wild like those of a madman, and he almost foamed at the mouth like a boar. At this I took such a hatred against temper as to wish never to be seen disgracing myself in one.

Restrain and hide your anger within yourself. For though one cannot become void of anger by the mere wish, one can control the unseemly manifesations of this passion.—Galen

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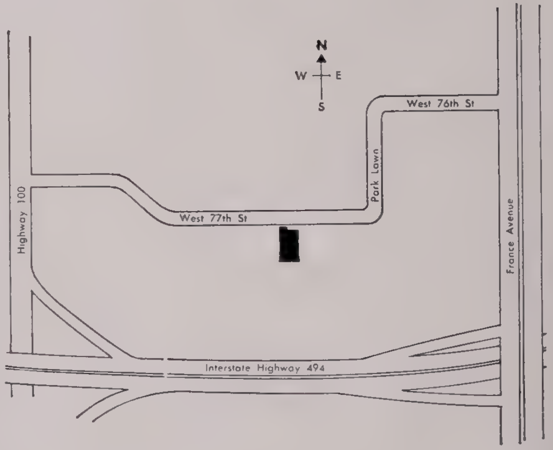

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As pointed out in the paper by Loken and co-workers, labeling the plasma is of use in diagnosing the cause of vaginal bleeding in the third trimester. We also have found such techniques particularly important in localizing the placenta prior to amniocentesis for transuterine fetal blood transfusion.

Technically, the test is fairly simple to perform, particularly insofar as the patient is concerned. A simple injection into the antecubital vein is virtually all that is needed. Then she has but to lie under a scintigraphic apparatus. For the physician it is somewhat more difficult in that human serum albumin must be labeled with pertechnetate ion in the laboratory. Owing to its short half-life, the labeled material must be used immediately. Sterility and pyrogenicity tests are of value only in retrospect.

While of unquestioned value, it is not necessary to employ a scintillation camera to perform such tests. Higher resolution scans may be obtained with more conventional rectilinear scanners. The chief potential advantage offered by the camera is that one might possibly avoid the necessity to retard the disappearance from the plasma of the radioactive medium by attaching it to a protein.

High degrees of accuracy have been reported by several workers in the field. Even so, it is not a static procedure. The use of many other compounds with even shorter half-lives than that of 99m-technetium is being explored. Were the test to remain at its current stage of development, however, it has already an important niche in the obstetrician's diagnostic armamentarium.

W. Newlon Tauxe, M.D.
Rochester, Minnesota

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*Loken, M. K., Dunham, C., and Spellacy, W. H.: Placental Localization: The Use of Technetium^{99m} Albumin and the Scintillation Camera. Minnesota Med 51:907, 1968.

Test Your Word Score

Falciform—*sickle-shaped* (page 214).

Involucrum—*a sheath, such as contains the sequestrum of a necrosed bone* (page 223).

Ergotropic—*pertaining to the reaction of the body cells to the application of nonspecific agents* (page 240).

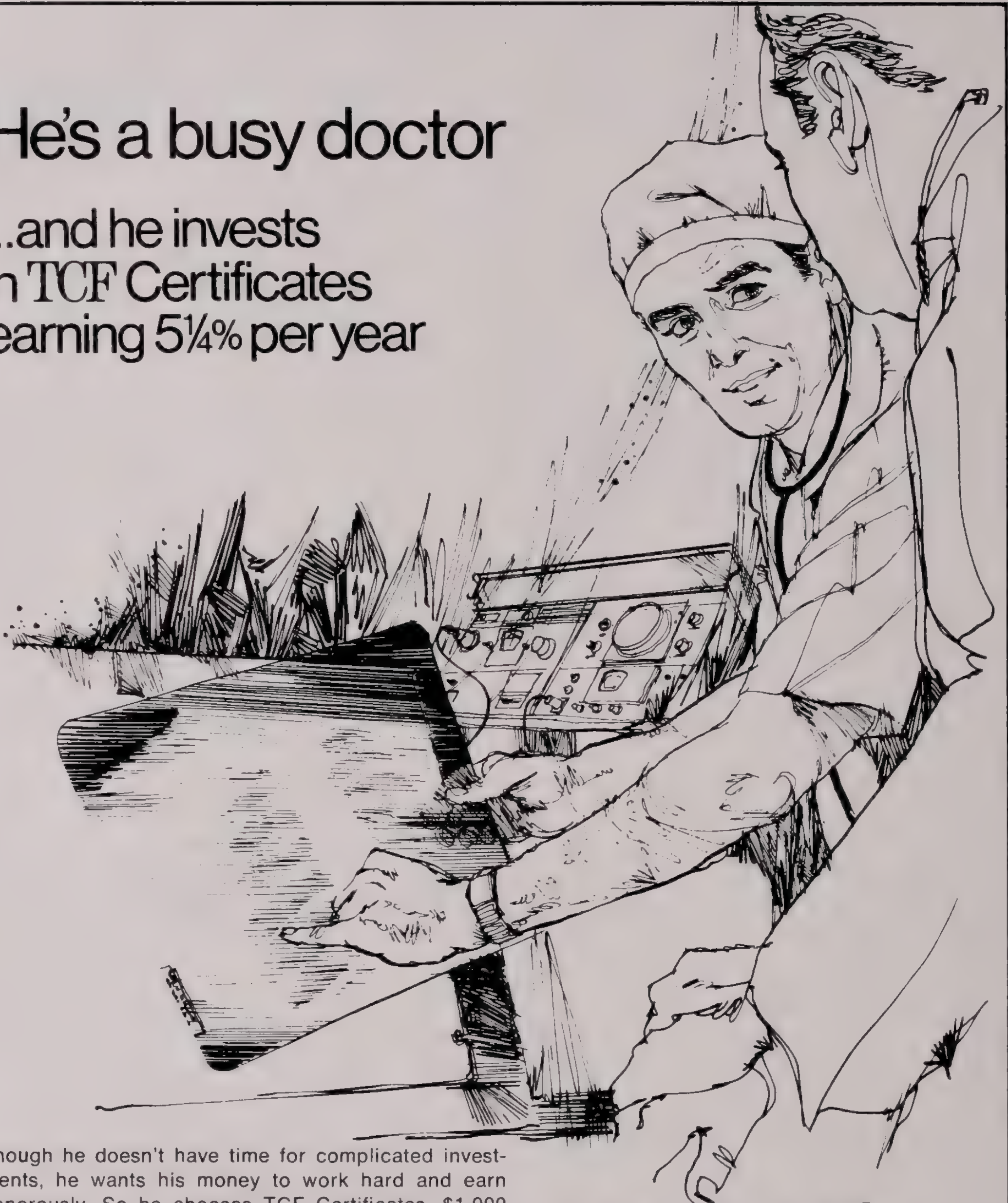
Trophotropic—*pertaining to the orientation of cells toward nutritive material* (page 240).

Autosomal—*characteristic of a paired rather than a sex chromosome* (page 243).

Métis—*half breed* (page 246).

A Conservative

A conservative is a man with two perfectly good legs who, however, has never learned to walk.—Franklin D. Roosevelt



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On the basis of the hypothesis that there may be a disturbance in the vitamin B6 metabolism in pregnancy, and that isoniazid-induced peripheral neuropathy[1,2,3,4] can be prevented by the administration of pyridoxine hydrochloride, one hundred milligrams of pyridoxine hydrochloride was administered intramuscularly to 23 pregnant women complaining of cramps, and this gave relief of cramp symptoms within 48 hours in all 23 patients.

In the past year .1 to .2 units of lidocaine 2% was added to the pyridoxine hydrochloride in order to relieve the pain of injection.

I therefore suggest that this method of treatment for leg cramps be carried out empirically by other physicians in order that larger clinical experience can be gained.

R. J. Thurn, M.D.
Duluth, Minnesota

Editor's Note: The above is an excerpt from Dr. R. J. Thurn's original, scientific manuscript. The paper was sufficiently documented with reference to its title, and all twenty-three patients with leg cramps who were treated by pyridoxine injection had resolution of their cramps. Ideally a tryptophane load test before and after treatment and also on a control non-cramp group would be included. It must be pointed out that Dr. Thurn is in general practice and does not have a clinical laboratory at his disposal. There is no better proof than his success.

References

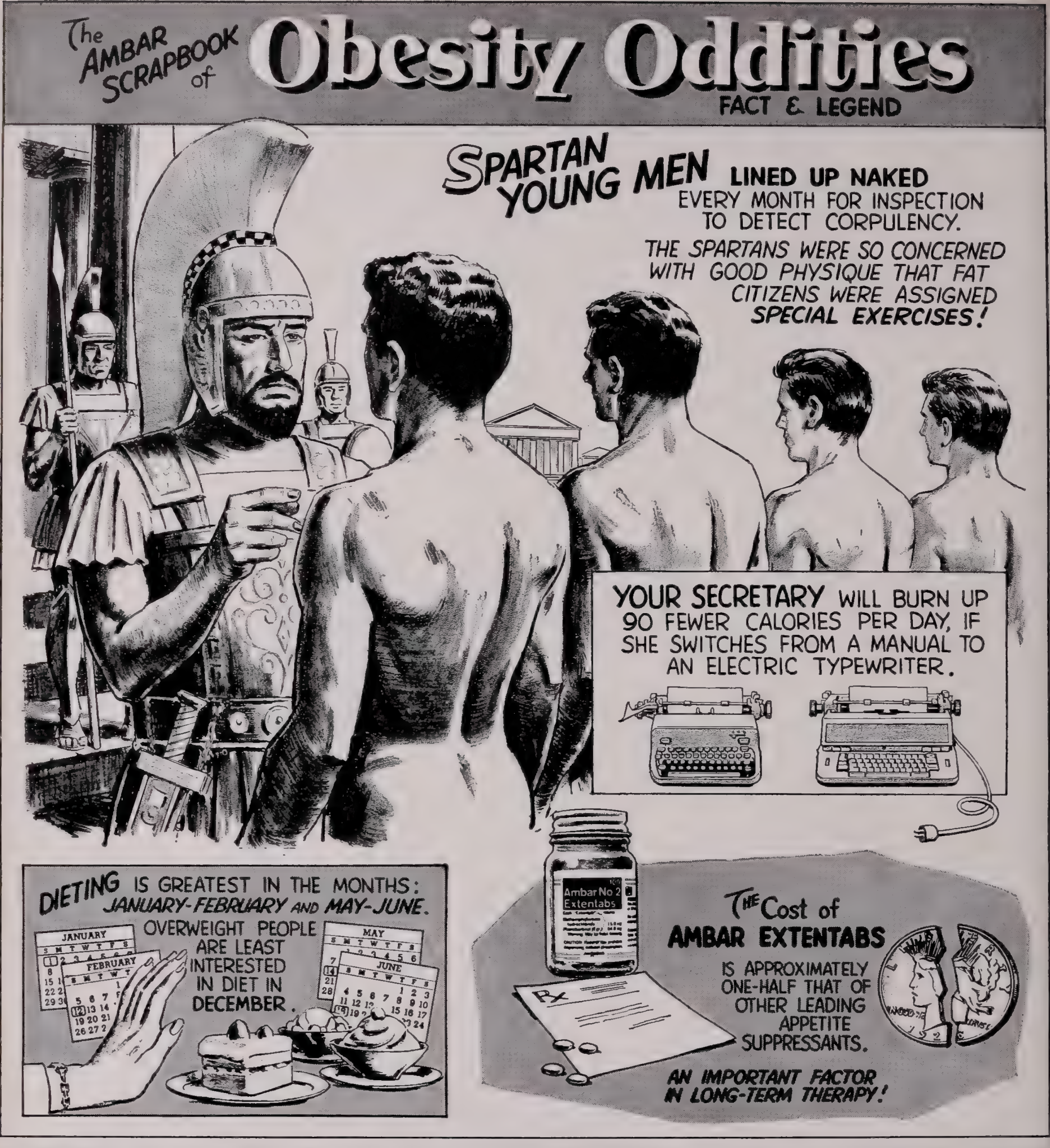
1. Page: Obstet Gynec 1:94, 1953.
2. Wachstein: J Lab Clin Med 40:550, 1952.
3. Gamon: Arch Neurol 70:64, 1953.
4. Ross: JAMA 1958.

Letter to the Editor

General Practice in Rural Ireland

Ireland is comprised of the Irish Republic (26 counties), an independent state, and of Northern Ireland (6 counties) which is part of the United Kingdom. The Health Service in Northern Ireland is part of the British National Health Service; medical services are provided by the State for persons of all income levels. These services are provided free of direct charge to the patient. Doctors in General Practice are paid on a capitation basis.

In the Irish Republic, General Practitioner services are provided free to the lower income group by the State. This group is composed of those who are medically indigent. These services are provided through a Dispensary System. The type of life which a General Practitioner leads depends on whether he is in Dispensary or private practice or both, and, whether he is in a predominantly rural or urban area. For example, the small town where I work has a population of about one thousand and a hinterland con-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taining two villages and many small farms, adding a further two thousand persons. I am in private general practice and also provide service to the lower income group as the District Medical Officer.

There is one Dispensary in my own town, Athboy, and one at Ballivor seven miles away. These small clinics consist of a consulting-cum-dispensing room and a waiting room. They are staffed by myself and a nurse. Four Dispensary sessions are held each week. Patients are seen, treated and the required drugs dispensed. Domiciliary calls are made to patients if necessary.

There is no local hospital and all cases, both medical and surgical requiring investigation or in-patient treatment, are referred to the appropriate consultant at our County hospital which is ten miles away, or to a Dublin hospital thirty miles away. There is a Maternity unit in a neighbouring town seven miles away and most patients are delivered there or in one of the Dublin Maternity hospitals. Nowadays domiciliary delivery is rare; 95% of all deliveries are in hospitals.

In Ireland medical services are midway between the free enterprise system obtaining in the U.S. prior to Medicare and total government control as in the British National Health Service. General Practitioners in their private practices are paid directly by the patient, though some patients recoup part of their fees from the Voluntary Health Insurance Agency. This is a State, non-profit, voluntary insurance scheme (like Blue Cross). For his Dispensary work the Practitioner is paid a salary by the local Health Authority. This is a fixed annual salary which bears no relation to his work load or to the number of services he is called upon to provide. The office of District Medical Officer is called a "part-time appointment" though he is bound by contract to provide twenty-four hour care. In the time not actually taken up by his Dispensary patients he must, of necessity, supplement his income by seeing private patients. These are seen at the doctor's office, usually in the afternoon and provided with domiciliary visits when required. My private office is situated in my home. Many patients are attended in their homes and at least one third of every working day is spent doing house calls!

The spending of so much time doing house calls will doubtless seem very strange to our American colleagues. It should be pointed out that until recently only a relatively small proportion of the population had motor cars, and public transportation in many rural areas is unsuitable and frequently inconvenient for patients. The pattern of practice is gradually changing with the realisation by the public that the doctor can give superior service at his office. In spite of this change, doctors are often called twenty-five miles or more, at odd hours on the most frivolous calls—"Mrs. Murphy has a sore leg, Doctor." This might be a deep vein thrombosis, but is more likely to be a varicose ulcer which she has had for several months!

The present system is in its dying stages and the Government has published a White Paper giving details of a proposed new service. The basic policy of the Government is to substitute for the Dispensary system a service with the greatest practicable choice of doctor and least practicable distinction between private and public patients. It is still proposed to confine State General Practitioner services to about 40% of the population. The Department of Health favours payment in this new service on a capitation basis, while the Profession are unanimously seeking payment on a fee per item of service basis. It is felt that experience in the United Kingdom and elsewhere has shown that the capitation method of payment does not foster a good

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doctor-patient relationship. Also, under capitation the doctor contracts to give unlimited service for a limited fee and is without redress if the calls made upon him are excessive.

The Profession believes in the concept of the patient's individual responsibility to provide health service for himself and his family, and fears an extension of the present State service from the 40% already covered to cover for the whole population. Two of the three major political parties are committed to such an extention.

It is noted in other European countries that the Health Service usually started on a limited scale and has been gradually extended to large sectors of the public. If this is to be the case in Ireland a system whereby the more affluent patient would pay at least part of his fee would seem to be most desirable. In some other countries it is apparent that it has become increasingly difficult for the family doctor to establish a personal relationship with each patient. In Ireland this has never been a problem and it would be a tragedy for Irish medicine if increasing State intervention were to upset the delicate balance between doctor and patient.

D. Waldron-Lynch, M.D.
Athboy, Ireland

President's Letter (Continued from page 209).

task of furnishing the superior quality of training for increased numbers of technologists that will unequivocally qualify them to relieve the harried radiologist of some of his more routine functions.

My musings must be brought to a close, and perhaps this can be most effectively accomplished by voicing the impression that radiology has passed from childhood to youthful maturity as a medical specialty. Certainly it has become one of the axes upon which medical practice not only rests but revolves. Nevertheless, I believe one can predict that the applications and techniques of radiology in the next decade will advance so dramatically as to defy comprehension by most of us today.

Martin Van Herik, M.D.
President
Minnesota Radiological Society

A wise man sees as much as he ought, not as much as he can.—Montaigne

All men are ordinary men; the extraordinary men are those who know it.—Chesterton

When a man say him do not mind, then him mind.—Negro proverb

There are three kinds of brains: one understands of itself, another can be taught to understand, and the third can neither understand of itself nor be taught to understand.—Niccolo Machiavelli

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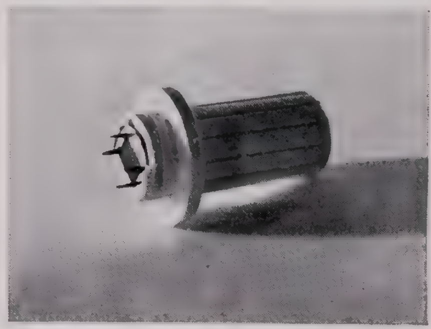

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The Editor's Soliloquy

"Watching" A Breast Tumor?

CONTRARY TO THE time-honored legal dictum that declares a man innocent until proven guilty, a breast tumor can never be considered innocent per se until it is unequivocally diagnosed and out. The diagnosing physician may justifiably regard himself as having a high degree of clinical acumen, based on observation and experience; but his judgment—as well as the new-in-vogue mammogram, echogram and thermogram— can never be infallible, because medical science, though progressively more precise and accurate, is not a mathematically exact science, but always involves the indeterminate and elusive doctor-patient equation. Hence a mistake in a clinical diagnosis can be justified as human error, and though it may not exceed two or three percent, that small deviation can still account for the unpredictable difference between life and death for some individuals.

Nothing is more distressing than to encounter a patient who says that her physician is "watching a breast tumor!" Periodic breast examinations are commendable; but to "watch" a breast tumor is a dangerous medical practice—all the more so because the patient has probably been "watching" her own breast tumor for a month or two before consulting her physician. One wonders: Does she finally seek professional advice merely for assurance that her "watching" tactics are defensible? Or, in her understandable apprehension, does she want someone to "watch" with her—in the hope that two persons "watching" will be more effective than just one person? Unfortunately no amount of "watching" can dematerialize a tumor!

A physician can almost always identify the physiologic breast lobulation that varies from the normal and differentiate between a slight deviation on the one hand and a tumor on the other. If he cannot distinguish with certainty he will seek consultation; he surely will not "watch" the suspected aberration—no matter how inconsequential it may seem.

Cystic disease of the breast may vary in its palpability from time to time and needle aspiration of the cystic fluid does not guarantee the absence of covert malignancy. The physiologic variation in the breast's degree of induration, which may be cyclic, should be evident within 14 days; therefore to "watch" a breast tumor for more than two weeks appears tantamount to waiting for an unequivocally positive diagnosis.

Numerous studies have indicated that radical removal of breast cancers, without demonstrable metastases, carries an infinitely better prognosis than when the lymph-nodes are involved. The patient or the doctor who is doing nothing more than "watching" a breast tumor may thereby be guilty of changing the prognosis irreversibly from favorable to unfavorable.

Either a breast tumor is obvious or it is suspicious. Only when no tumor can be palpated is the physician justified in recommending periodic examination alone. He cannot "watch" a breast tumor!—

Carl O. Rice, M.D.

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Warning: In renal impairment, usual doses may lead to excessive accumulation and liver toxicity. Under such conditions, lower than usual doses are indicated, and, if therapy is prolonged, serum level determinations may be advisable. A photodynamic reaction to natural or artificial sunlight has been observed. Small amounts of drug and short exposure may produce an exaggerated sunburn reaction which may range from erythema to severe skin manifestations. In a smaller proportion, photoallergic reactions have been reported. Patients should avoid direct exposure to sunlight and discontinue drug at the first evidence of skin discomfort. Necessary subsequent courses of treatment with tetracyclines should be carefully observed.

Precautions: Overgrowth of nonsusceptible organisms may occur. Constant observation is essential. If new infections appear, appropriate measures should be taken. In infants, increased intracranial pressure with bulging fontanels has been observed. All signs and symptoms have disappeared rapidly upon cessation of treatment.

Side Effects: Gastrointestinal system—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocol
pruritus ani. Skin—maculopapular and erythematous rashes; a r
case of exfoliative dermatitis has been reported. Photosensitiv
onycholysis and discoloration of the nails (rare). Kidney—rise in B
apparently dose-related. Transient increase in urinary output, so
times accompanied by thirst (rare). Hypersensitivity reactions—u
caria, angioneurotic edema, anaphylaxis. Teeth—dental staining (
low-brown) in children of mothers given this drug during the latter
of pregnancy, and in children given the drug during the neonatal p
od, infancy and early childhood. Enamel hypoplasia has been see
a few children. If adverse reaction or idiosyncrasy occurs, disconti
medication and institute appropriate therapy. Demethylchlorte
cycline may form a stable calcium complex in any bone-forming tis
with no serious harmful effects reported thus far in humans.

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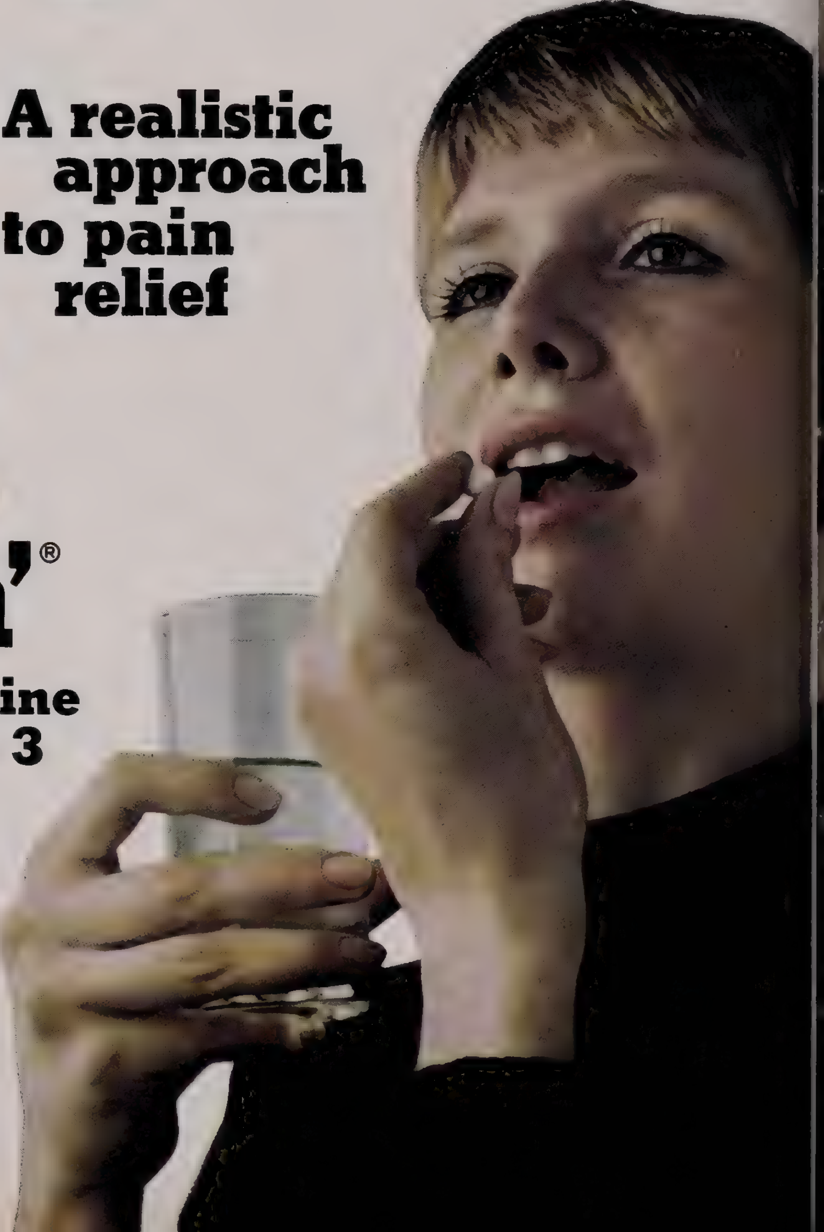

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Curbstone Consultation

INTRATHORACIC TUMOR

QUESTION: I referred a three-and-a-half-year-old child for removal of an intrathoracic tumor. Surgery was abandoned because of bleeding after only partial removal of the tumor. Repeated histologic sections showed the tumor to be benign ganglioneuroma. Although the child continues to do well I am concerned as to what the future course of management should be. What potential exists that this tumor may degenerate, for example, into a malignant neuroblastoma if left alone?

ANSWER: Although malignant neuroblastomas may mature into benign ganglioneuromas (or even eventually progress to scar tissue) there is no evidence that the reverse occurs. Partially removed ganglioneuromas ordinarily cause no further symptoms, and watchful waiting is all that is indicated in such cases.

Harold D. Kletschka, M.D.
Houston, Texas

LANGER'S ARCH

QUESTION: What is Langer's arch and is it of any clinical significance?

ANSWER: Langer's arch results from an anomalous muscle which traverses the axillary cavity extending from the lateral border of the latissimus dorsi to the undersurface of the insertion of the pectoralis major. It probably occurs in about five percent of individuals, but in only a relatively small percentage is it developed to such an extent as to be of clinical importance. The chief clinical significance of this structure is that when presenting as a mass in the axilla, this anatomic variation must be differentiated from pathologic conditions in that region. This structure may lead to confusion in such operations as radical mastectomy if the surgeon is unaware of its existence.

He who laughs frequently is kind and genial in all things and is not worried over trifles. He who laughs rarely is contrary and critical.
—*Gilbertus Anglicus (Doctor Desideratissimus) (1180-1250)*

Laboratory Letter

The Pill and Protein Bound Iodine and T-3 Results

Occasionally a physician has asked me why protein bound iodine and T-3 results don't jibe in women on oral contraceptives. What brands, he wanted to know, were responsible? How high did drugs push the protein bound iodine? How much could they depress the T-3? How should he approach thyroid function in women on hormones?

All good questions. Here is a go at the answers. First, though, a few scraps of important information: (1) Most thyroxine binds to globulin in serum; less than 0.1% goes unbound, or "free," (2) Protein bound iodine measures mostly the iodine attached to this globulin. (3) The amount of globulin inversely affects the T-3 value (the more globulin circulating, the less radioactive tri-iodo-thyronine "taken up"). When a woman takes birth control pills, estrogen in the pills increases that portion of protein to which thyroxine clings, thereby forcing the protein bound iodine up and the T-3 down.

To get at the other answers, I recently went over the drug histories of 50 women on contraceptive pills who had high protein bound iodines and low T-3s. Types of pills included C-Quens, Enovid and Enovid-E, Norinyl and Norinyl-1, Ortho-Novum, Ovulen, and Provest. Thus, all the commonly used agents exerted a thyroid effect. And a significant one, too. Values for protein bound iodine ranged from 8.1 mcg.% to 21.0 mcg.% (mean 10.1 mcg.%) and for T-3 from 24% to 8% (mean 19%).

Yet when I multiplied protein bound iodine by T-3 to get a Free Thyroid Index:

$$\underset{(4\text{-}8\ \text{mcg.}\%)}{\text{Protein Bound Iodine}} \times \underset{(25\text{-}35\%)}{\text{T-3}} = \underset{(100\text{-}280)}{\text{FTI,}}$$

48 patients fell into the euthyroid range. From this and other studies, I am convinced the Index reliably measures thyroid status when patients have drug or disease-induced protein charges.

Up to this point, I have not mentioned two other serum tests: T-4 by column chromatography and "free" T-4 by a mixed isotope dilution method. In our laboratory, the T-4 column test, though accurate and precise enough, has not solved the pill problem. Like protein bound iodine, estrogen sends it up. And like protein bound iodine, drugs containing organic or inorganic iodine, will cause high results. Theoretically, "free" T-4 ought to be the answer since globulin changes do not influence it. But it is more expensive than a protein bound iodine and T-3 together, gives about the same information[1] and, at least in the Mayo Clinic experience, "distinguished poorly between different levels of thyroid function."[2]

Richard L. Reece, M.D.
Minneapolis, Minnesota

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Middle Age: When you begin to exchange your emotions for symptoms.
—*Irvin S. Cobb*

The Viewing Box

Mass Behind the Heart

THIS 53-YEAR-OLD MAN was hospitalized with a chief complaint of hematemesis and melena. The patient's history included recurring, intermittent jaundice and bouts of cholangitis for 30 years. Cholecystectomy was performed in October 1967, at which time a liver biopsy revealed biliary cirrhosis.

Presently, the patient has cholangitis, edema of the lower extremities, and ascites. Physical examination revealed deep jaundice and a spleen enlarged to three fingerbreadths below the left costal margin; the liver was not enlarged.

What is your diagnosis? (See next page.)

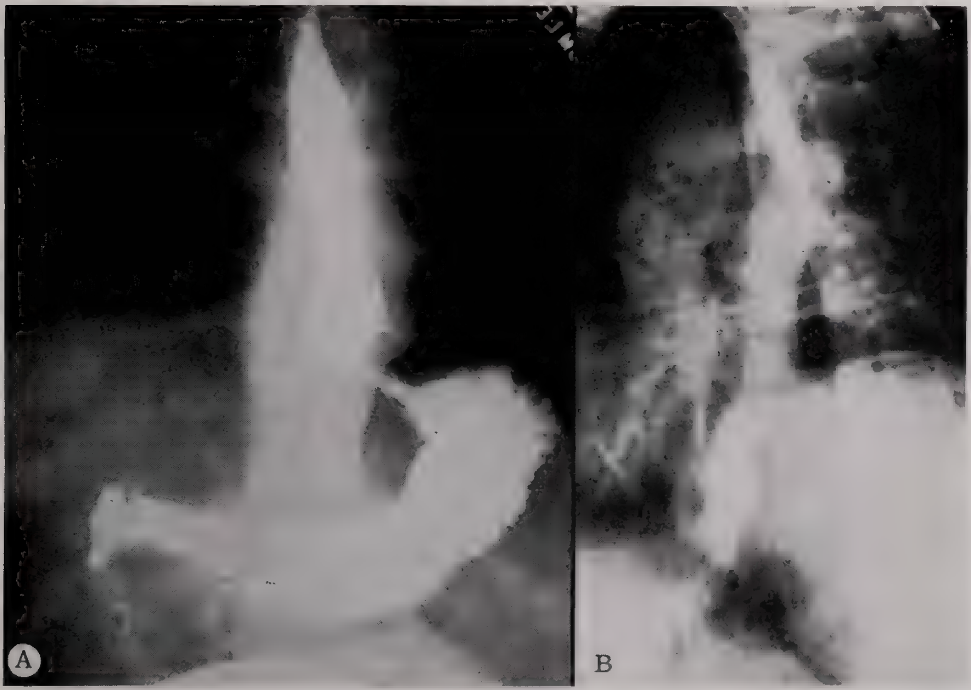

Fig. 1—(*A*) and (*B*), Barium examination of esophagus October 26, 1967, revealed a mass closely associated with the lower esophagus, deviating it anteriorly just above diaphragm. In addition, evidence of calcification in right upper quadrant was noted.

Diagnosis: Massive esophageal varices. Extrahepatic portal vein obstruction.

Comment

Most esophageal varices are associated with portal venous hypertension secondary to intrahepatic obstruction. The most common cause of intrahepatic obstruction is long-standing hepatic cirrhosis. Extrahepatic obstruction produced by thrombosis of the portal vein, pancreatitis, or extrinsic compression is rare by comparison.

Esophageal varices may be present with either intrahepatic or extrahepatic obstruction, as flow in the portal system away from the liver into the systemic veins ("hepatofugal" flow) occurs with both. In extrahepatic block, the blood flow through collateral channels bridging the obstruction in the portal vein is inadequate to decompress the proximal portal venous systems.

The first examples of the radiographic diagnosis of esophageal varices were published by Wolf[1] in 1928 in a case of syphilitic involvement of the liver and spleen. He noted circumscribed, translucent areas on the posterior wall of the esophagus. The patient later died of hemorrhage. Kirklin and Moersch[2] found similar filling defects in the lower esophagus that were associated with portal hypertension and hepatic cirrhosis.

The diagnostic accuracy of the barium examination of the esophagus in the detection of esophageal varices is limited. Reports indicate an accuracy of this procedure in the range of 25 to 50%.[3,4] Percutaneous splenoportography with serial filming during a period of at least 12 seconds is the most reliable radiologic examination for the detection of esophageal varices. During this procedure, measurements of splenic pulp pressure can be made easily. Usually, splenoportography reveals the anatomy of the portal vein system and the changes thereof in enough detail for the surgeon to decide on the operability of the patient and to choose the type of operative procedure.

The unusual aspects of this case include: (1) the enormous size of the collateral channels; (2) the sparseness of the collateral channels at the lower esophagus, instead of the many vessels usually present with portal obstruction; (3) the absence of the characteristic submucosal filling defects in the lower esophagus on the esophagogram; (4) the extramural position of the varices, as seen on the splenoportogram; and (5) the simulation of a mass

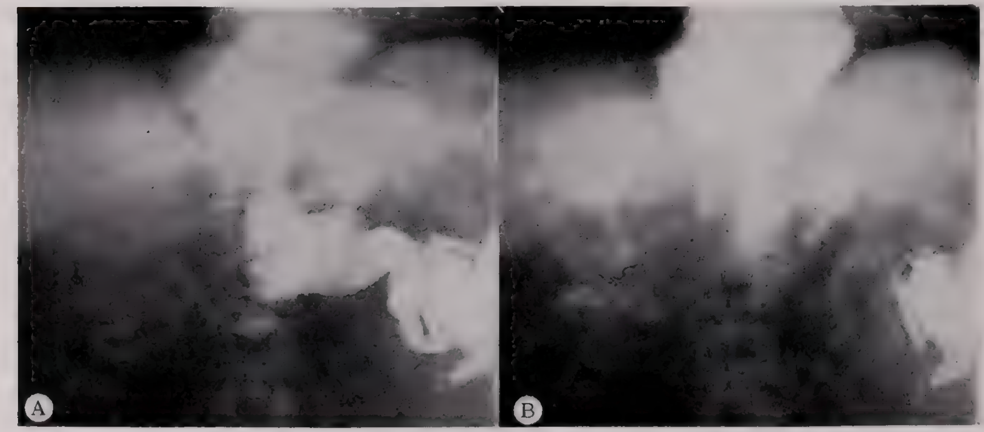

Fig. 2—Percutaneous splenoportogram on February 2, 1968, revealed a dilated splenic vein. (*A*), Bulk of contrast medium subsequently filled huge tortuous cardiac veins in lower esophageal region. (*B*) Film reveals hepatic radicals filled with medium from collateral network, indicating extrahepatic portal vein obstruction. Splenic pulp pressure was elevated to 38 cm. of water.

in the mediastinum, with deviation of the esophagus anteriorly.

Differential diagnosis of the esophagogram includes aneurysm of the lower thoracic aorta and paraspinal abscess or mass.

Bizarre submucosal defects caused by esophageal varices have been reported, including some defects that have been mistaken for malignant lesions of the lower esophagus or stomach.[5] However, we could not find any reports of extramural varices that have produced detectable changes on the esophagogram.

Complications of portal hypertension are well known; the most serious include hematemesis, pancytopenia, and death. Prompt diagnosis and treatment can be life-saving. Various surgical procedures have been performed, but the creation of a shunt between portal and systemic venous circulation has proved to be the most helpful.

David M. Rulfs, Jr., M.D.*
Franz J. Hallermann, M.D.†
Rochester, Minnesota

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*Mayo Graduate School of Medicine (University of Minnesota), Rochester: Resident in Radiology.
†Mayo Clinic and Mayo Foundation: Section of Roentgenology.

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For Diseases of the Fundament

For diseases of the fundament, a sovereign remedy is bear's gall, mixed with the grease; to which some persons are in the habit of adding litharge and frankincense. Butter, too, is very good, employed with goose-grease and oil of roses. Bull's gall upon lint is a remarkably useful remedy, and has the effect of making chaps of the fundament cicatrize with great rapidity. Bear's blood is curative of inflamed tumours and apostemes upon these parts in general; as also bull's blood, dried and powdered. The best remedy, however, is considered to be the stone which the wild ass voids with his urine, it is said, at the moment he is killed. This stone, which is in a somewhat liquefied state at first, becomes solid when it reaches the ground: attached to the thigh, it disperses all collections of humours and all kinds of suppurations: it is but rarely found, however, and it is not every wild ass that produces it, but as a remedy it is held in high esteem.—Pliny

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Confusion

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Fracture Conference

Posttraumatic Affections of the Metacarpal Joints of the Thumb

Dr. Paul R. Lipscomb:*

Injuries to the thumb are not rare, and usually our attention is directed to this area after an acute injury, though it is possible to see the patient for the first time after repeated exposure to minor trauma, which may result in early degenerative changes at the base of the thumb, with crippling hand symptoms.

Case 1

Dr. Rogers C. Southall:†

This 43-year-old meat-packer had been seen at our institution in 1953 because of fatiguing of her thumb and prominence of the base of the thumb for the preceding three years. Some atrophy was also noted. In 1962 she returned with weakness and numbness in the median distribution of her hand, thenar atrophy, and an adduction contracture of the first metacarpal (Figure 1 *A*).

Dr. Lipscomb:

I think you can see on the roentgenogram the subluxation of the first metacarpal on the trapezium. We could not get a history of a specific injury; yet this is true of many patients that have the localized type of degenerative change. We proceeded with an arthrodesis, because this woman needed to use her thumb in her work. She was 43 years old, with many years of work still ahead of her.

Dr. Southall:

The postoperative films (Figure 1 *B*) show the thumb after surgery to the first metacarpo-carpal joint. She also had section of the transverse carpal ligament to decompress the median nerve in the carpal tunnel. This was done bilaterally.

Fracture conference held April 24, 1968.

*Professor of Orthopedic Surgery, Mayo Graduate School of Medicine (University of Minnesota), Rochester and Consultant, Section of Orthopedic Surgery, Mayo Clinic, Rochester.

†Resident in Orthopedic Surgery, Mayo Graduate School of Medicine, (University of Minnesota), Rochester, Minnesota.

Dr. Lipscomb:

Three months after surgery she returned to work. Her work in the meat-packing plant required a strong pinch and grasp; hence the arthrodesis. In older women I think that excision of the trapezium is probably just as good a procedure as arthrodesis, provided the cartilage is still present over the distal end of the navicular.

Dr. Southall:

Five years later when she returned to our clinic (Figure 1 *C*) she still had thenar atrophy, but she was relieved of pain and numbness in her hands.

Dr. Lipscomb:

Many of these symptoms, of course, are due to traumatic arthritis as a consequence of injuries to the metacarpal trapezial (metacarpal greater multangular joint).

Dr. Mark B. Coventry:*

This seems to be almost exclusively a female disease, and I wonder if it might be due to the relaxed connective tissues that women have, as opposed to men. I don't think I have ever seen symptomatic degenerative arthritis of this joint in a male.

Dr. Lipscomb:

This is true of the type that we have shown here; the males we have seen with these degenerative changes do give a history of injury, usually a fracture. However, I have seen a man, who was also a packing-house worker, with essentially the same condition as has just been described. Perhaps it

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*Associate Professor of Clinical Orthopedic Surgery, Mayo Graduate School of Medicine (University of Minnesota), Rochester, and Consultant, Section of Orthopedic Surgery, Mayo Clinic, Rochester, Minnesota.

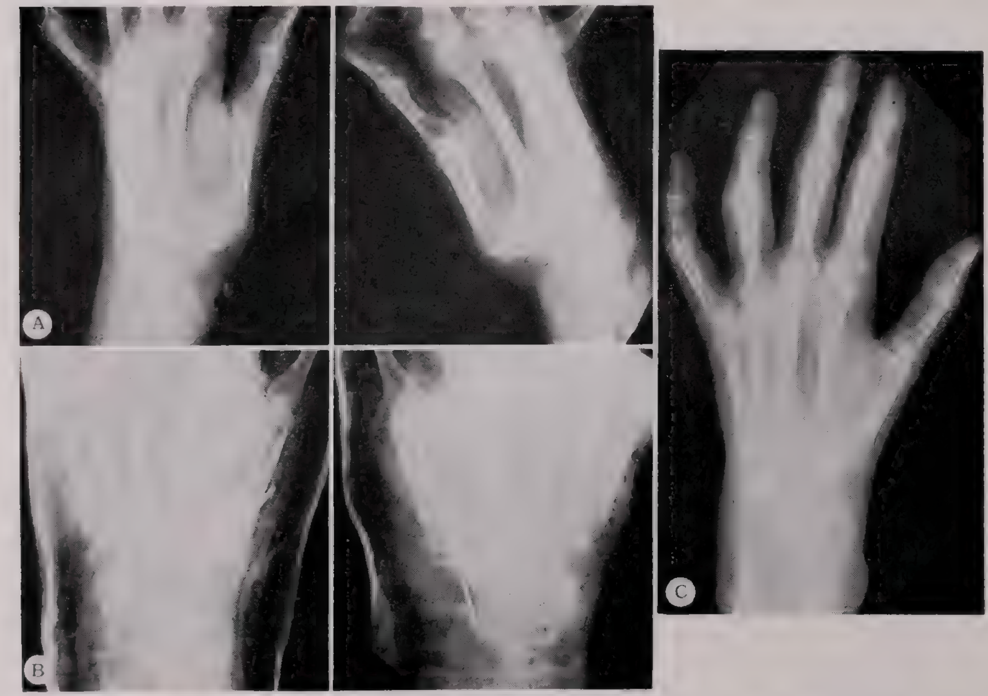

Fig. 1 (Case 1)—(A) Preoperative, showing degenerative arthritis of metacarpo-carpal joints. (B) Postoperative, showing arthrodesis of first metacarpo-carpal joint, with crossed Kirschner wires for fixation. (C) Five years later, showing fusion of metacarpo-carpal joint of left hand. In the interval, destructive changes developed in the fourth proximal interphalangeal joint, suggestive of rheumatoid arthritis.

is like rheumatoid arthritis, which is more common in women, five to one. There are so many of these conditions that are associated with metabolism of collagen tissues. It is not a true degenerative phenomenon, but trauma does contribute.

Case 2

Dr. Southall:

The next patient is a 50-year-old clinic consultant who was Indian wrestling with his son when his thumb was forced into radial abduction and he felt a sudden "pop." He noticed swelling and instability of the metacarpophalangeal joint. A diagnosis of rupture of the ulnar collateral ligament of the metacarpophalangeal joint of the thumb was made.

Dr. Lipscomb:

He had too much pain to place stress on the site of injury when I was examining him in the office, but I could demonstrate definite instability. These injuries usually produce a rupture of the collateral ligament on the ulnar side of the thumb. Occasionally an injury will rupture the radial collateral ligament rather than the ulnar collateral ligament. Rupture of the latter is a common injury; sometimes, the adductor tendon gets caught in the joint and then surgery is necessary.

Dr. Southall:

The discussion was whether to treat him with a gauntlet cast or by a method that would allow him to have his thumb free. It was elected to use two pins across the joint to immobilize it (Figure 2). These Kirschner wires were removed a month later, and the patient started mobilizing his thumb.

Dr. Lipscomb:

He continued to practice in a way that he said he couldn't have done if a cast had been applied. He had tenderness where the ends of the Kirschner wires had been buried beneath the skin and said that if he had to go through it again, he would prefer the cast; but if he had elected the cast originally, I suspect he would have wanted it this way. I did not repair the ligaments

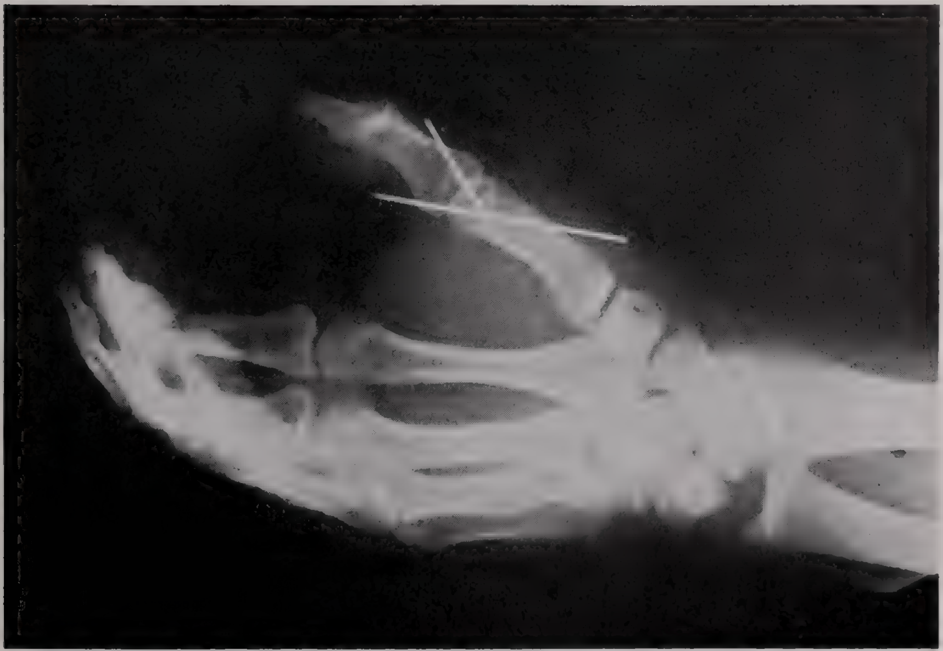

Fig. 2 (Case 2)—Kirschner wires immobilizing metacarpophalangeal joint of thumb.

on the ulnar side of the first metacarpo-carpal joint, because this was an acute injury, and I thought that with approximation of the ends of the torn ligament and firm fixation it would heal without actual surgical repair.

Case 3

Dr. Southall:

The next patient is a 27-year-old bricklayer who fell from a scaffold in April 1967 and injured his left thumb. Thereafter he complained of "looseness" (as opposed to his other thumb) and instability. He had normal flexion and extension. At his work he found that he was unable to pick up bricks or cement blocks. In September 1967, a roentgenogram showed how wide the thumb could be abducted (Figure 3). These, you will note, are stress films.

In September 1967, the ulnar collateral ligament was exposed surgically and was found to be avulsed from the proximal phalanx and curled upon itself. It was resutured to the proximal phalanx after two Kirschner wires had been inserted to ensure immobilization. Approximately one month later the wires were removed, and the patient was noted to have good stability at the site of injury. Three months later he returned to work. About six months after surgery, when he returned for reexamination, he complained of some stiffness in this joint and moderate pain when lifting heavy cement blocks. However, there was no instability.

Dr. Lipscomb:

The point we would like to make here is that we did not repair the ligaments and then insert the Kirschner wires. We put the wires in to hold the joint in normal position and then repaired the ligament. This was a very unstable situation, and it would have been impossible to tack and hold the

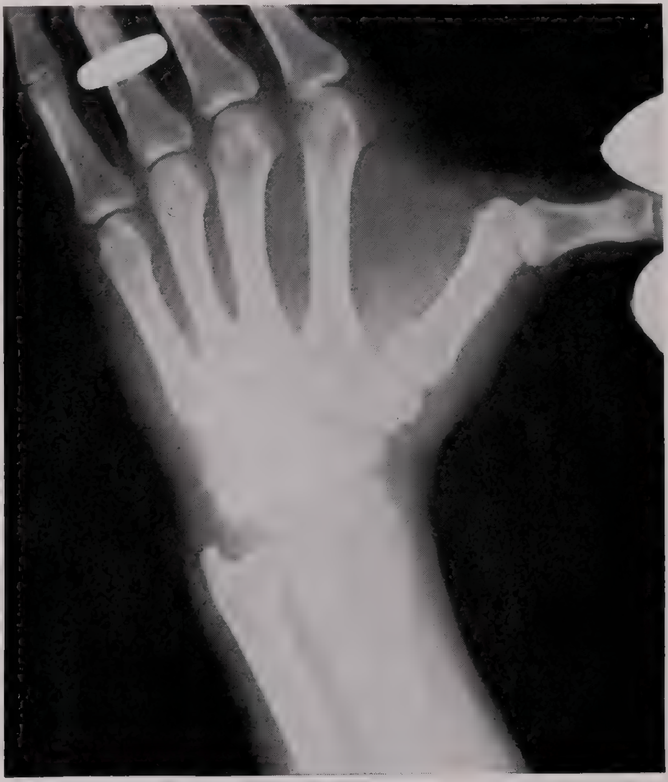

Fig. 3 (Case 3)—Stress film, left thumb.

ligament with sutures unless the joint was first fixed very securely. The injury involved the man's left hand, and he said that he had no trouble when he picked up bricks, but when he picked up heavy concrete blocks all day long, he naturally had some stiffness and soreness in this joint. I suspect that this would be true no matter how the ligaments were fixed. Time will determine whether he will continue to have trouble. If he has enough pain, I suspect the only thing to do next would be to arthrodese the joint, but we wouldn't want to do that unless we absolutely had to.

Case 4

Dr. Southall:

The next patient is a laborer who, in November 1964, fell on his left hand and suffered a fracture (Figure 4). This is a Bennett's type fracture, at the base of the first metacarpal, with lateral subluxation of the metacarpal on the trapezium. The fracture was easily reduced by applying traction to the thumb and forcing the shaft of the metacarpal inward. However, the reduction was unstable until two Kirschner wires were placed across the base of the first metacarpal for the purpose of immobilization.

Dr. Lipscomb:

I think we can just show these examples and hurry along because Dr. Southall has prepared a brief discussion of one of the means of treating this injury. A month later the wires were removed, and since then the patient has had good function.

Case 5

Dr. Southall:

The next case is that of a 27-year-old resident at our clinic who fell on the ice and then noted tenderness at the base of his first metacarpal. The roentgenogram (Figure 5 *A*) shows the fracture and subluxation of the base of the metacarpal.

Dr. Lipscomb:

In the next film (Figure 5 *B*) you can see better the small fragment that is displaced. Because he was a surgical resident, it was important to avoid the development of traumatic arthritis later. I could not get this reduced by traction and abduction of the thumb.

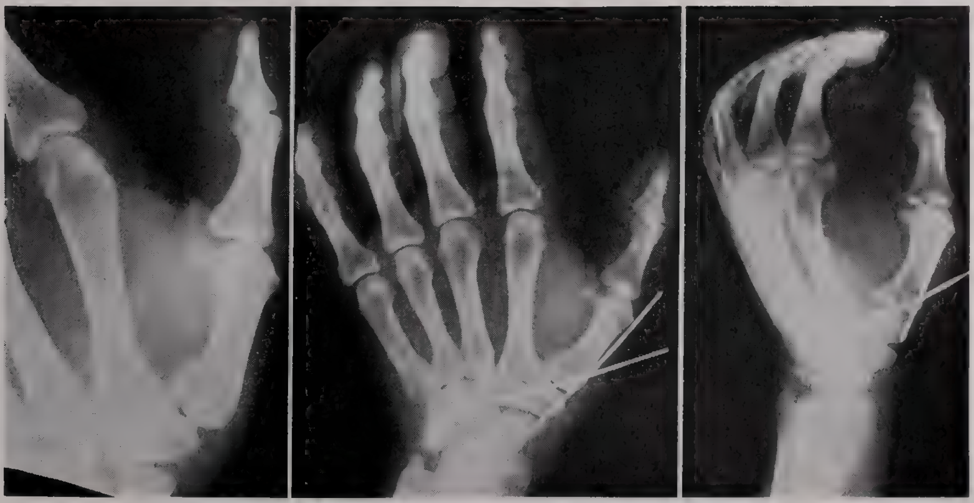

Fig. 4 (Case 4)—Bennett's fracture before and after closed reduction.

Dr. Southall:

He was placed in a cast from the distal phalanx to the midforearm, with the thumb in abduction. The following day the metacarpal of the thumb seemed to have displaced more, and skeletal traction through the distal phalanx was instituted. A 20-gauge needle was placed through the distal phalanx to act as a ferrule, and a loop of 28-gauge stainless steel wire was

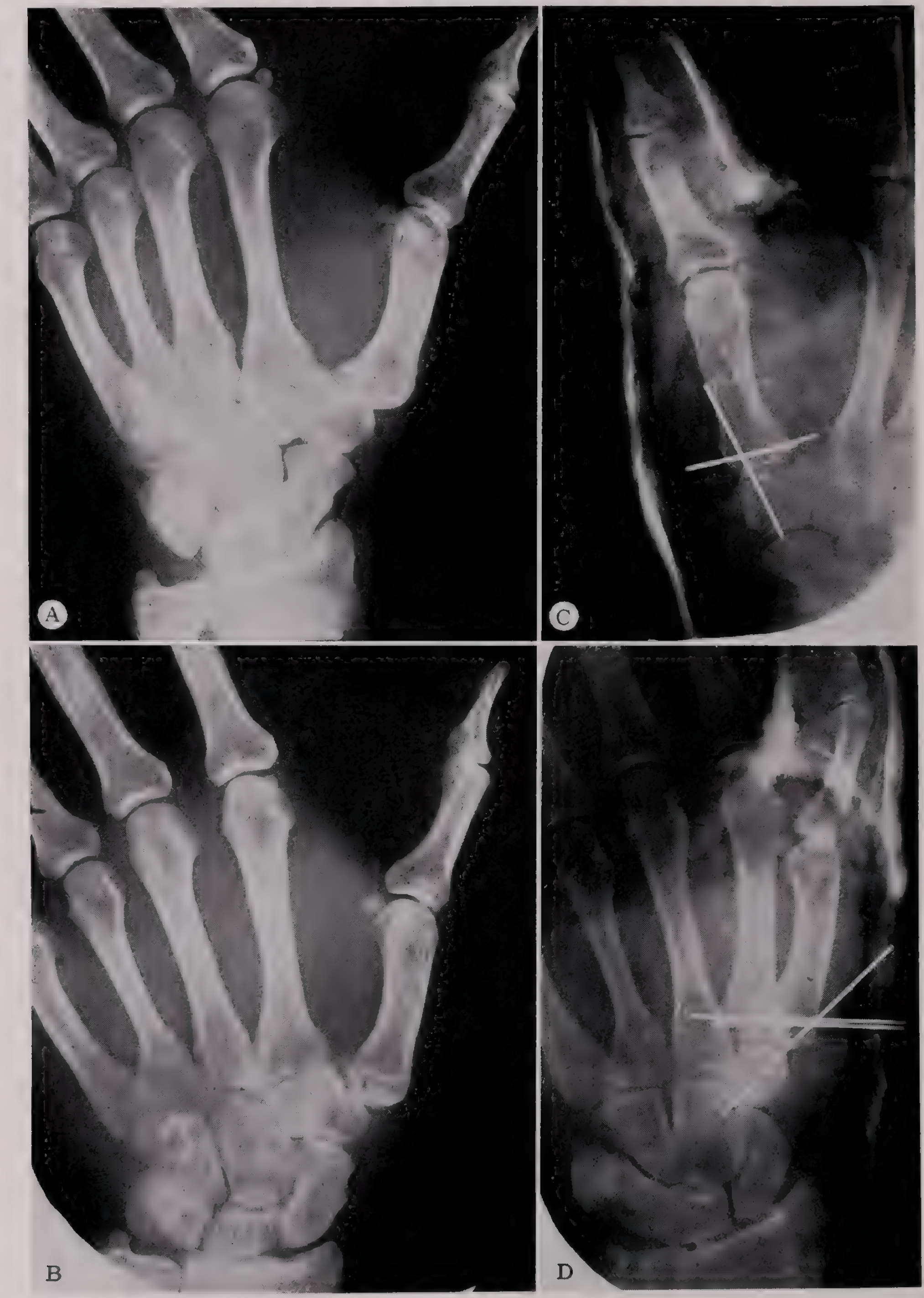

Fig. 5 (Case 5)—(A) Fracture dislocation of base of first metacarpal. (B) Preoperative position. (C) and (D) Immediately after open reduction (through cast).

threaded through this. A rubber band was attached to the loop, and an outrigger made from a coat-hanger wire was incorporated in the cast. Three days later there was still no reduction. Approximately a week after the injury, open reduction was done, and the base of the shaft of the metacarpal was pinned to the small fragment of bone with Kirschner wires (Figures 5 *C* and *D*). A month later the wires were removed (Figures 6 *A* and *B*). These roentgenograms (Figures 6 *C*, *D*, and *E*) show the function and range of motion 14 months after surgery; he had no pain at this time, and as far as we know has had no further trouble. I now want to say a few words about the Bennett fracture.

Bennett's Fracture

Dr. Southall:

Fracture subluxation of the metacarpal of the thumb was first described by Bennett in 1882. This type of fracture is most commonly the result of a fist fight. The patient strikes his opponent with his clenched fist, and the metacarpal is forced into flexion, thereby fracturing the anterior margin of the metacarpal; the remainder is then displaced backward and proximally on the trapezium. The condition also results from falls and injuries in sports. Because of the anatomic features of the first metacarpo-carpal joint, this

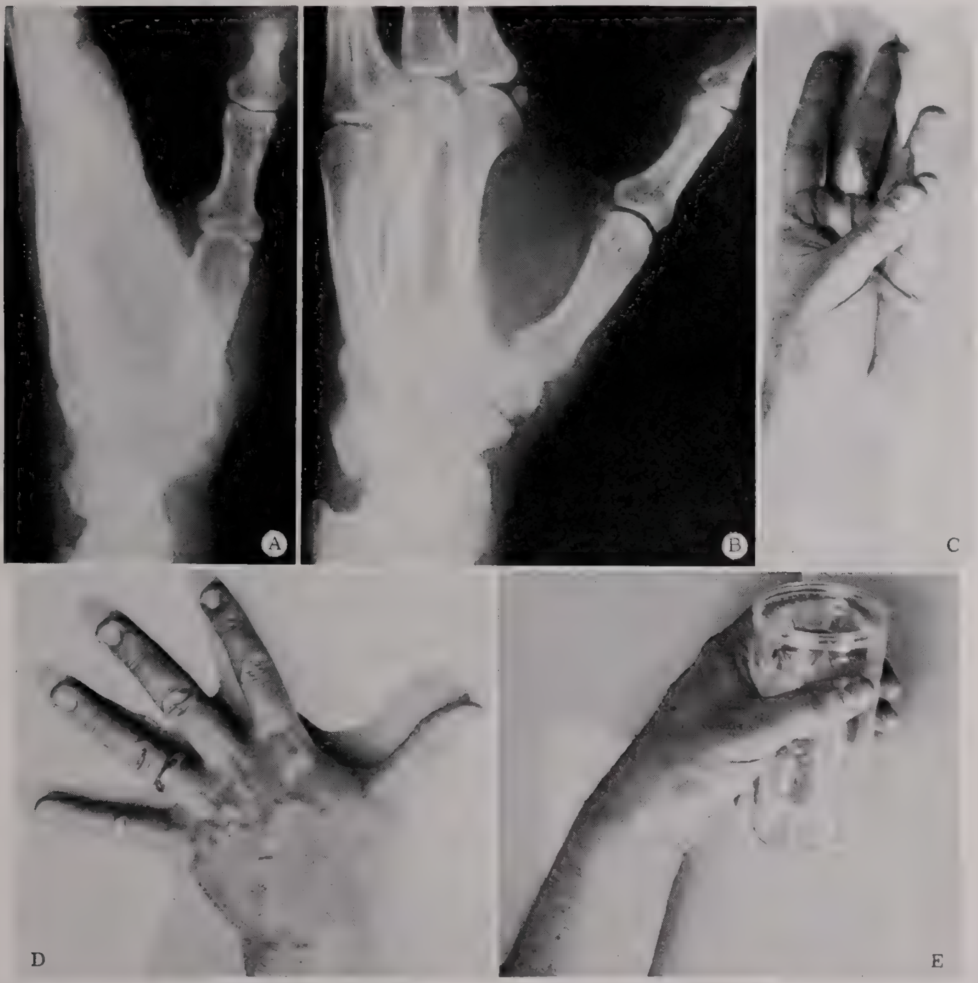

Fig. 6 (Case 5)—(A) and (B) One month after open reduction. (C), (D) and (E) Function of thumb 14 months after reduction.

fracture is easy to reduce but difficult to retain in reduction. Bennett was the first to be disappointed with the results of treatment. The end result of poor reduction may be a painful, tender swollen joint and pain on grasping. The criteria of treatment should be both anatomic and functional. There may be a poor correlation between the anatomic result as judged from the roentgenogram and the functional result as judged by the patient and his physician. There are multiple methods to maintain reduction.

First Method of Maintaining Reduction

The first is closed reduction and the use of a cast to maintain the position. Pollen[1] reduced the fracture dislocation by pressure at the base of the thumb, and then held this digit in abduction and extension and, while maintaining this position, placed the patient's thumb in an unpadded cast from the distal phalanx to the upper forearm. He reviewed the results in 31 patients and found that 29 were successfully treated. All of these patients returned to work within four months after removal of the cast. Probably the most important criterion of success is based on the patient's ability to return to his former occupation. Bennett attributes failure of the closed method to the physician's unfamiliarity with the treatment of this fracture. It is not a common fracture, and very few physicians accumulate a large experience.

Second Method

The second method depends on closed reduction and skeletal fixation. Johnson,[2] in 1944, described a method whereby reduction was stabilized by passing two wires through the metacarpal of the thumb into the metacarpal of the index finger. In 1950, Wagner[3] described a method in which he passed a wire through the base of the metacarpal into the trapezium and thereby transfixed the joint. We saw an example of this technique in Case 4.

Third Method

The third method is based on open reduction. This was first described by Lambotte[4] in 1913; he transfixed the fragments with a small nail. Disagreement exists as to which method of treatment is the best. Gedda,[5] in 1954, stated that anatomic reduction was essential for good function. Others, such as Griffiths[6] in 1964, showed that malunion is compatible with good function, although not invariably.

When deciding which method to use, we believe the surgeon should employ the technique most likely to produce and maintain anatomic reduction and, by doing so, assure an acceptable functional result, which should not be marred by development of traumatic arthritis years later, if this complication is preventable. Certainly this complication should be decreased by an anatomic reduction and healing.

Conclusion

Dr. Lipscomb:

Fracture dislocation of the base of the metacarpal of the thumb is named Bennett's fracture after Edward Hallaran Bennett of Ireland. He became Professor of Surgery at the age of 36 and, in this capacity at Trinity College in Dublin, amassed a remarkable collection of cases involving fractures, dislocations, and bone diseases. His original description of this fracture dislocation was based on five cases and was published in 1882. Even though he had no roentgenograms to guide him, his description is still accurate today.

Repeated minor episodes of trauma to the first metacarpo-carpal joint eventually may produce deformity of the thumb and disabling symptoms, and may require surgical treatment—either arthrodesis of the joint or removal of the trapezium. This seems mostly a problem of women.

Traumatic rupture of the ligaments stabilizing the metacarpal phalangeal joint of the thumb occurs, and the physician should be aware of this possibility. Good stabilization of the joint is necessary for sound healing of its ligaments. Failure to get adequate healing produces an unstable joint, a weak pinch, and eventual degenerative changes with pain.

Bennett's fracture dislocation is seen mostly in men, results from acute trauma, and is sometimes difficult to treat because it is unstable. Dr. Southall has discussed three basic methods of dealing with this problem. There is no doubt in my mind that if reduction is not accurate and well maintained, degenerative changes in this joint will result in time.

Paul R. Lipscomb, M.D.*
Rogers C. Southall, M.D.†
Einer W. Johnson, Jr., M.D.‡
Rochester, Minnesota

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6. Griffiths, J. C.: Fractures at the Base of the First Metacarpal Bone. J Bone Joint Surg 46B:712, 1964.

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A fanatic is one who can't change his mind and won't change the subject.—Winston Churchill, 1952

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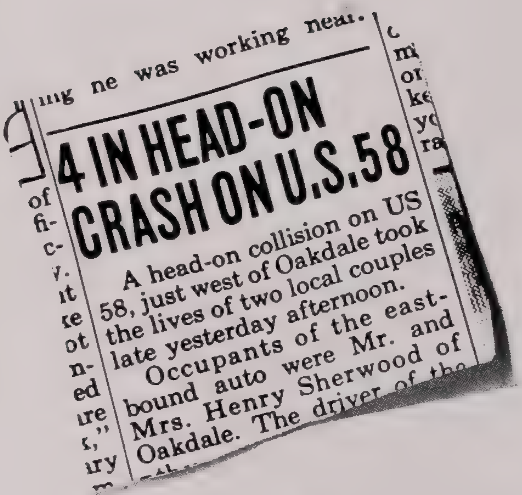

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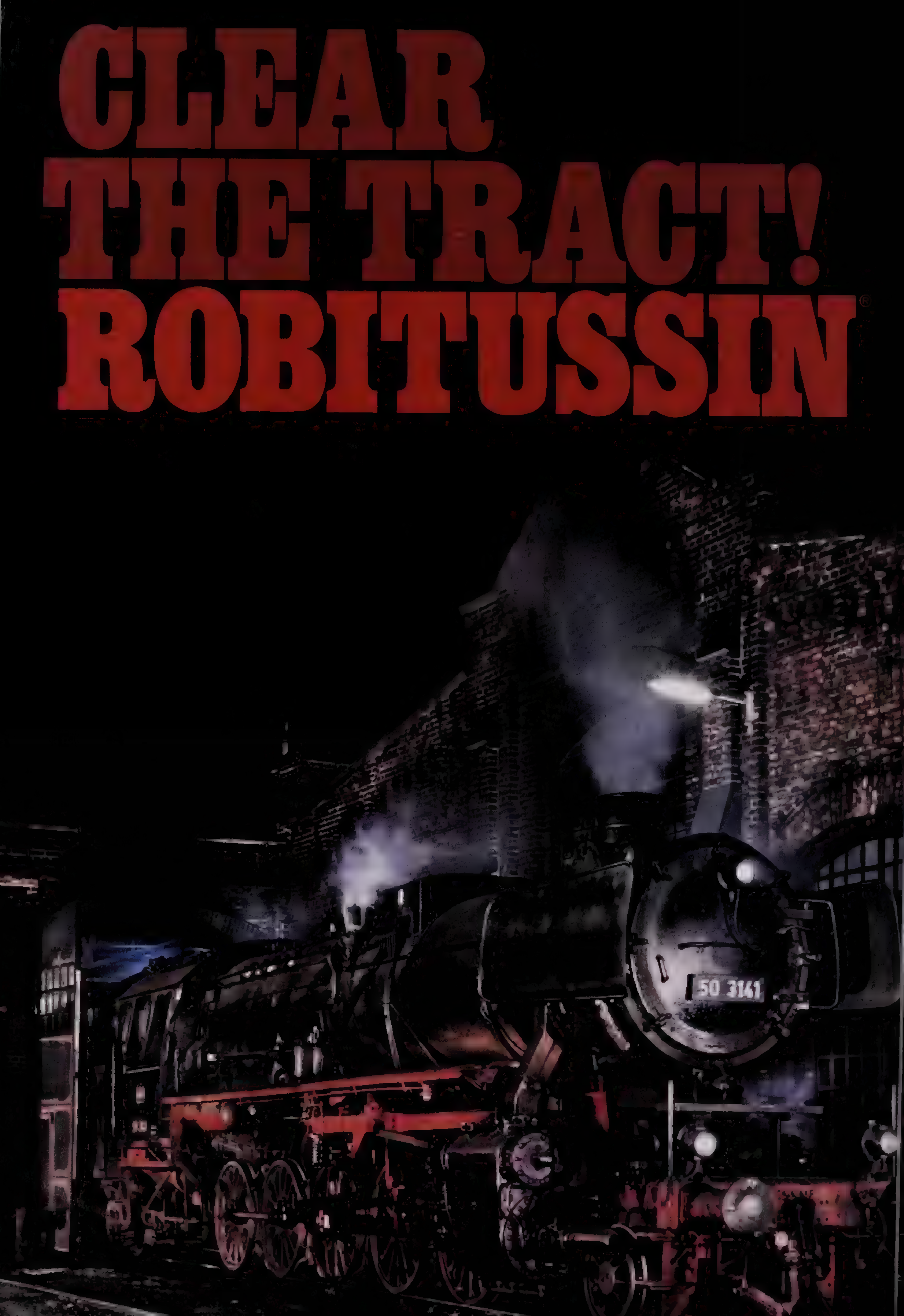
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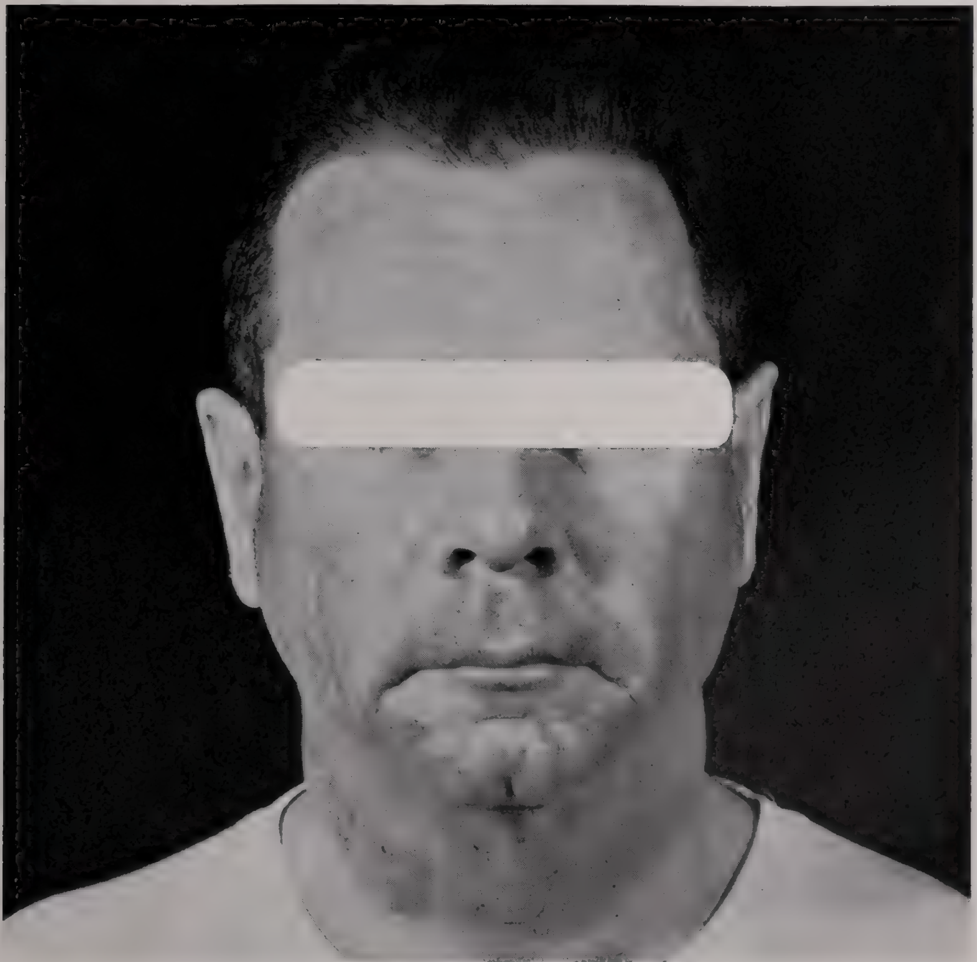
Dermatology

Cutaneous Light Sensitivity Due to Fluorescent Lights

In the past the physician was secure in the fact that his patients who had cutaneous light sensitivity would have a dermatitis only during the late spring, summer, and early fall. During the other periods of the year, the patient could return to a normal existence, engage in outdoor activity, and be free of dermatitis.

Environment

In the last 20 years, with the introduction of the fluorescent lamp, man changed significantly his indoor-light environment. Fluorescent light contains visible light and little infrared radiation; however, there are significant amounts of ultraviolet light (without far ultraviolet—sunburn wave-



Figure

lengths). Depending upon the energy (voltage) input into the bulb, the ultraviolet output may be quantitatively small or very great. Most light sensitivity eruptions are triggered by wave lengths in the ultraviolet region. Fluorescent bulbs can emit enough quanta of ultraviolet light to precipitate a dermatitis in a patient with a cutaneous light sensitivity. We can no longer be secure in our question, "Does your dermatitis appear in the spring, get worse in summer, and disappear in the fall?" Freedom from dermatitis in the colder months of the year is no longer a significant clinical finding in the diagnosis of light-sensitivity dermatitis. A careful history must be taken to evaluate the indoor light environment of the patient, both at home and at work, in order to define the total light exposure a patient has in his daily routine.

Clinical

The clinical expression of the disease will depend upon the amount of clothing worn and the amount of exposure to fluorescent lighting. The distribution of the eruption may be very bizarre, depending upon the location and use of the fluorescent light. For example, if the fluorescent light is a reading lamp, the eruption may be one-sided. Clinically the eruption looks like a contact dermatitis with sharp outlines from the protective effect of the clothing. The full spectrum of the primary clinical lesions may be present (from erythema to vesicles); however, usually erythema, papules or eczema-like eruptions are more common. Bullous lesions are rare. As the eruption becomes chronic, lichenification can take place.

Treatment

In the treatment of the patient, it may be necessary to remove the fluorescent lights in his home. If there is fluorescent light exposure at work, he may have to work under incandescent light or even change jobs. Protective sunscreen ointments may afford sufficient protection to allow the patient to work under minimal fluorescent exposure. By reducing the amount of fluorescent light exposure during late fall, winter, and early spring, some patients who have light sensitivity aggravated by fluorescent lighting can be free of their disease during this period.

Ramon M. Fusaro, M.D., Ph.D.
Minneapolis, Minnesota

Unity of the Individual

Why do doctors so often make mistakes? Because they are not sufficiently individual in their diagnosis or their treatment. They class a sick man under some given department of their nosology, whereas every invalid is really a special case, a unique example. How is it possible that so coarse a method of sifting should produce judicious therapeutics? . . . The principal grievance which I have against the doctors is that they neglect the real problem, which is to seize the unity of the individual who claims their care.*

---

*Amiel, H. F., in Richard Magraw: Ferment in Medicine, 1966.

The passion for setting people right is an afflictive disease.—Marianne Moore

Tumor Conference

Mesenteric Cysts

BENIGN MESENTERIC cysts comprise less than 1.0% of acute abdominal emergencies. A report of one such interesting case and a discussion of benign alimentary cysts follow.

Case Report

A seven-year-old white female was seen in the Emergency Room of St. Mary's Hospital, Duluth, Minnesota, on June 16, 1968, with complaints of abdominal pain 12 hours prior to

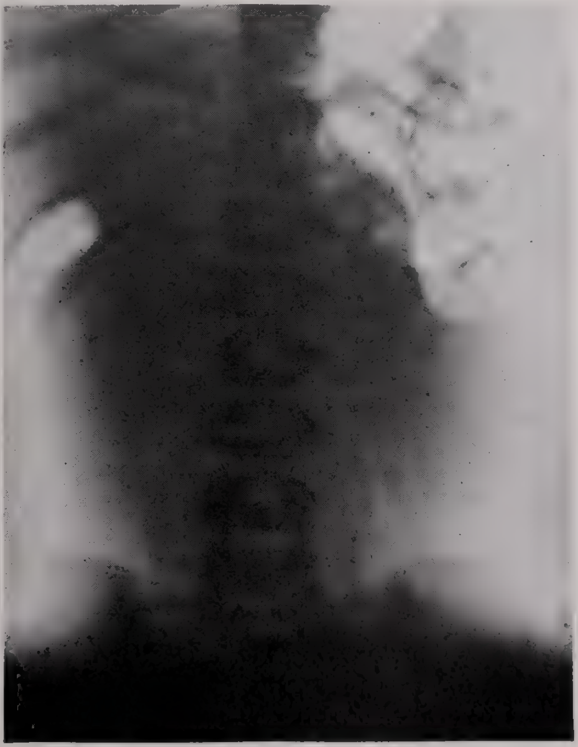


Figure 1

admission, associated with nausea and vomiting, the latter not relieving the distress. Past medical history revealed only chronic obstipation unrelieved by cathartics.

Physical examination revealed a seven-year-old girl acutely and chronically ill with a blood pressure of 110/80, a pulse rate of 98, and a temperature of 100.8. The positive physical findings, confined to the abdomen, showed moderate distention, marked pain on palpation in the right lower quadrant, with rebound but without rigidity. The bowel sounds were diminished. Rectal examination was normal.

Laboratory studies: Hgb 10.8 gm, WBC 11,900, differential showing 70% PMN, 26% lymphs, 3% monos and 1% eosinophils. Urinalysis—specific gravity 1.026, albumin 0, sugar 0, microscopic examination normal.

A chest film was read as negative (Figure 1). An x-ray photofluorogram of the abdomen revealed a large cystic mass in the right abdominal cavity with viscera compressed to the left side.

Treatment

On the evening of admission the patient underwent abdominal exploration via a large transverse abdominal incision inferior to the umbilicus. A large, 2400-gm mesenteric "clover leaf" cyst of the mid-ileum was observed, intimately associated with the bowel, and was removed with resection of 17 cm of ileum. An incidental appendectomy was also performed, along with an open end-to-end entero-enterostomy. The child made an uneventful recovery, being discharged on the fifth postoperative day.

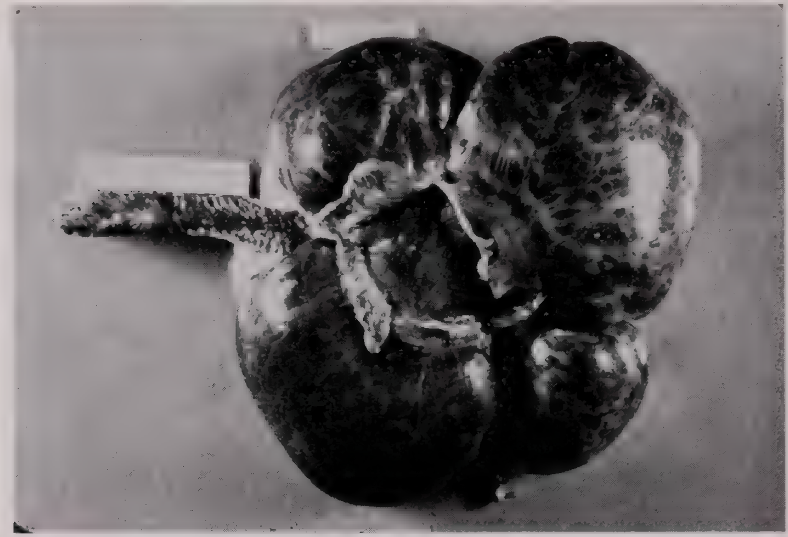


Figure 2

Pathology

A multiloculated cystic structure was present, located in the wall of the ileum, the locules intercommunicating with each other but not with the ileal lumen. Fluid content of the cystic structure revealed a hemoglobin concentration of 0.77 gm %, RBC 270,000/mm^3, WBC 2,300/mm^3 and a protein content of 3.5 gm %. The lining of the cystic structure had been destroyed and replaced by granulation and fibrous tissue with foci of cholesterol deposition and foreign-body reaction. Microscopically it could be demonstrated that the muscular wall of the adjacent uninvolved ileum had split, a portion continuing in the usual position in the segment of involved ileum, the outer half extending into and forming part of the wall of the cystic structure.

Discussion

Cysts of the mesentery are not rare lesions. In 1950 Beahrs reported approximately 600 such cases, with cystic lesions outnumbering solid ones by 2:1. The origin of mesenteric cysts still remains an enigma; but a classification from Lahey and Eikerson gives some indication as to the origin:

1. Wolffian cysts—remnants of the urogenital system
2. Lymphatic achylous cysts
3. Ectopic dermoid cysts
4. Mesocolic cysts—arising from rudiments of peritoneum
5. Parasitic or inflammatory cysts
6. Traumatic hemorrhagic cysts

One of the more comprehensive reviews of alimentary cysts by Kissane and Smith reveals these cysts to be most likely embryologically oriented. In reviewing the work of Lewis and Thyng, they noted that in the mammalian embryo of 4 mm to 23 mm the developing intestine has occasionally associated epithelial buds within the submucosa of the parent gut, which persist and may expand along the axis of the latter. The growth of the normal intestine at this time is so rapid that the common intestinal lumen to the "epithelial buds" may become focally occluded. When eventual vacuolization of the parent gut and the epithelial buds occurs, coalescence may not resume between the two future intestinal leaves; hence a persisting segment of vacuolated intestine or alimentary tract results.

One can readily see that most alimentary cysts may be explained by such mechanisms. The vast majority (76.0%) are seen in the intestine, most likely because of its greater length. In addition, because of the embryologic origin, the cysts may demonstrate any variety of duplication from complete segments of the alimentary tract to merely isolated multiloculated cysts that may, though usually do not, communicate with the parent bowel.

Complete surgical removal is axiomatic and, because of the degree of duplication that may be present, a complete search of the abdominal cavity for secondary cysts or "duplications" must be made during surgery.

Conclusion

A case of intestinal duplication in a seven-year-old girl has been presented. Excision of the cyst was performed for symptoms of acute right lower quadrant pain.

R. J. Campaigne, M.D.
Duluth, Minnesota

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There are three fields in which all human beings are credulous—money, matrimony and medicine.—Morris Fishbein

Things medical and gruesome have a singular attraction for many people.—William Osler

Help the Needy!

This patient may appear to "have everything" but, like so many people getting along in years, she may well be in need—*medically*. Though there is no evidence of organic disease, she does have symptoms (fatigue, vague aches and pains, malaise) that may be indicative of—

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Advance

Sensitivity of Klebsiella, Enterobacter, and Escherichia Coli to Cephalothin

CEPHALOTHIN (7-(THIOPHENE-2-ACETAMIDO)CEPHALOSPORANIC ACID) is related to penicillin in structure and in antibacterial activity. It has also been found to be very active against strains of *Proteus mirabilis* but less active against strains of the *Klebsiella-Enterobacter** group and *Escherichia coli.*[2] Recent reports have suggested the existence of considerable variation in the sensitivity of *Klebsiella* and *Enterobacter* to this antibiotic.[3-6] A discrepancy between the recommended 30-μg disc diffusion method and the tube dilution test was noted in this laboratory in regard to the sensitivity to cephalothin of strains of *Klebsiella, Enterobacter,* and *E. coli.* The purpose of this study therefore was to determine the extent of the discrepancy by performing the two types of sensitivity tests in parallel and to explore some of the factors which might contribute to the discrepancy.

Materials and Methods

Organisms

Two-hundred-five organisms, comprising 80 strains of *Klebsiella* spp., 80 of *E. coli,* and 45 of *Enterobacter* spp. were examined. All were isolated from fresh clinical material (specimens of sputum, urine, and feces; nasal, throat, and wound swabs; and blood cultures). The strains were tested for purity and identified biochemically by the methods of Edwards and Ewing[7] as outlined for routine laboratory use by Douglas and associates.[8] No attempt was made to assign the strains of *Klebsiella* to species or to serotype the strains of *E. coli.* The *Enterobacter* strains were assigned to species according to the procedure described by Edwards and Ewing.[7] There were 28 strains of *Enterobacter cloacae,* 16 of *Enterobacter aerogenes,* and one strain not assigned. As a control, a strain of *Staphylococcus aureus* with a stable sensitivity to cephalothin (minimal inhibitory concentration, 0.19 μg/ml) was included.

Antibiotic

Powdered sodium cephalothin (Keflin)* was reconstituted with sterile distilled water, diluted with trypticase soy broth (TSB) to a concentration of 1,000 μg/ml, dispensed in aliquots of 2.3 ml, and frozen at −20 C. Prior to use, an aliquot was further diluted with trypticase soy broth to a concentration of 200 μg/ml and serially diluted twofold in trypticase soy broth. Cephalothin discs (30 μg) were obtained commercially.†

Media and Assay Methods

Tube dilution tests were performed by the method of Grove and Randall.[9] Serial twofold dilutions of antibiotic in 0.5 ml of trypticase soy broth were seeded with 0.5 ml of a 10^{-3} dilution of an overnight trypticase soy broth culture of the test strain. The final concentration of antibiotic ranged from 50 to 0.39 μg/ml. After overnight incubation at 37 C, the minimal inhibitory concentration (MIC) was recorded as that amount of antibiotic producing complete inhibition of macroscopically visible growth.

Disc diffusion tests were carried out by a modification of the method described by Ericsson.[10,11] A 150 by 25-mm plastic Petri dish containing 40 ml of Mueller-Hinton (MH) agar was flooded with 4 ml of a 10^{-3} broth dilution of an overnight broth culture of the test strain. The plate was tilted and excess fluid was aspirated. Three cephalothin discs were spaced equidistantly on the plate and the antibiotic was allowed to prediffuse into the agar at room temperature for 30 minutes. The plates were then incubated at 37 C for 18 hours. The resulting zones of inhibition were measured with a pair of sliding calipers and the average of the three zones was recorded. If the difference between the three zone diameters on a single plate was greater than 2.0 mm, the test was considered to be inaccurate and was repeated.

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*Formerly called Aerobacter and now designated as Enterobacter according to nomenclature proposed by Ewing.[1]

*Eli Lilly and Company, Indianapolis.

†Baltimore Biological Laboratories, Baltimore.

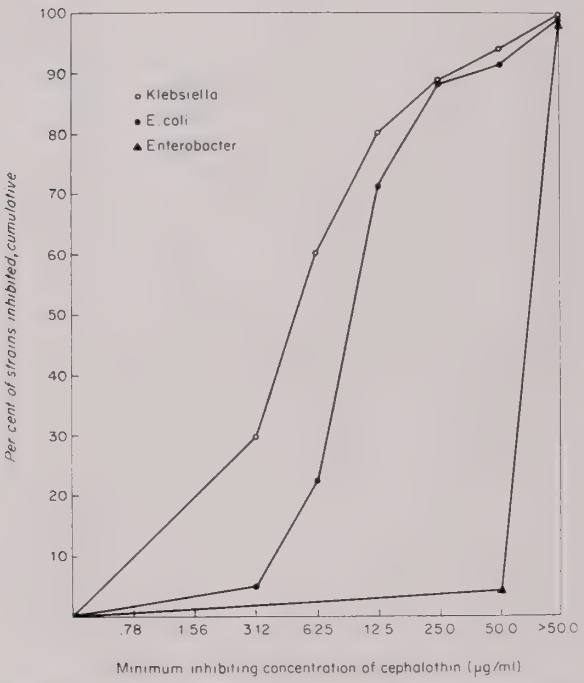

Fig. 1—Susceptibility of *Klebsiella, Enterobacter,* and *E. coli* strains to cephalothin (cumulative plot).

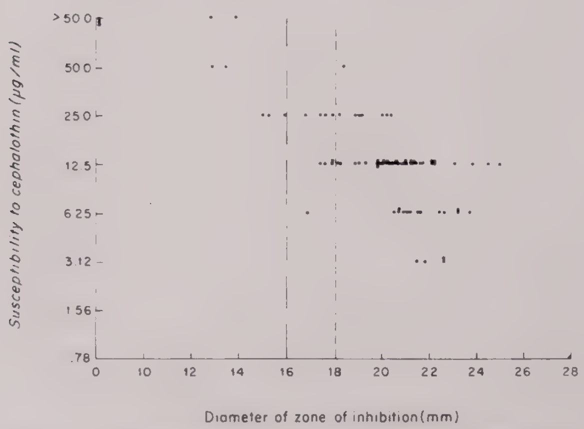

Fig. 2—Correlation of results of 30-µg disc and tube dilution sensitivity tests of 80 strains of *Klebsiella* tested against cephalothin.

To investigate the influence of different media on zone size, five *Klebsiella* spp. and six *E. coli* strains were chosen at random, and both the tube dilution and disc diffusion tests were repeated using three different media. Trypticase soy agar (TSA), trypticase soy agar with 5% rabbit blood (RBA), and Mueller-Hinton agar were used for the disc diffusion tests. Tryptose phosphate broth (TPO_4)*, trypticase soy broth, and Mueller-Hinton broth were used for the tube dilution tests. Readings were made at six, 12, and 20 hours during incubation at 37 C. Disc sensitivity tests were read at 18 hours.

Results

All 45 strains of *Enterobacter* had a minimal inhibitory concentration of 50 µg/ml or greater by the tube dilution method (Figure 1). However, seven strains exhibited zones of inhibition of 16 mm or greater, which is said to represent the minimal diameter for determination of sensitivity. These seven strains included two of *Enterobacter cloacae,* four of *Enterobacter aerogenes* and the one *Enterobacter* strain not assigned. Three strains of *Enterobacter aerogenes* had zones of inhibition of 11, 12, and 14 mm, respectively. The rest showed no inhibition.

For 64 (80%) of the 80 strains of *Klebsiella,* minimal inhibitory concentration was 12.5 µg/ml or less; for only nine (12%) was it 50 µg/ml or greater by the tube dilution method (Figure 1). With the 30-µg discs, 75 (94%) of the 80 strains exhibited zones of inhibition (of at least 16 mm), including seven strains with minimal inhibitory concentration = 25.0 µg/ml, three strains with minimal inhibitory concentration = 50.0 µg/ml, and one strain with minimal inhibitory concentration > 50.0 µg/ml (Figure 2).

For 59 (74%) of the 80 strains of *E. coli,* minimal inhibitory concentration was 12.5 µg/ml or less by the tube dilution method (Figure 1). With the 30-µg disc, 71 (89%) of the 80 strains exhibited zones of inhibition of at least 16 mm, including 11 strains with minimal inhibitory concentration = 25 µg/ml and 1 strain with minimal inhibitory concentration = 50 µg/ml (Figure 3).

---

*Difco, Detroit.

No difference in minimal inhibitory concentration related to composition of the medium employed in the tube dilution test was noted (Table 1). The "skipped tube phenomenon" described by Benner and associates[3] was noted with *Klebsiella* strain no. 899 in that at 12 hours there was growth in the tube with 6.25 µg/ml but not in the tubes with 3.12 or 12.5 µg/ml.

In disc sensitivity testing, use of 10^{-1} dilution resulted (not unexpectedly) in smaller zone diameters than with the 10^{-3} dilution (Ta-

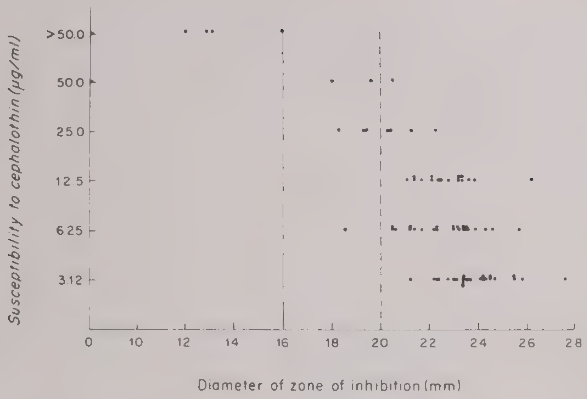

Fig. 3—Correlation of results of 30-µg disc and tube dilution sensitivity tests of 80 strains of *E. coli* tested against cephalothin.

TABLE 1

Effect of Three Different Broth Media on Tube Dilution Sensitivity of *Klebsiella* and *E. coli* Strains Tested Against Cephalothin

		MIC (µg/ml)								
	Strain	6 hours			12 hours			20 hours		
Organism	number	MH*	TSB	TPO_4	MH	TSB	TPO_4	MH	TSB	TPO_4
Klebsiella	577	3.12	1.56	1.56	6.25	3.12	3.12	6.25	6.25	3.12
	796	3.12	0.78	1.56	12.5	6.25	6.25	12.5	6.25	6.25
	714	1.56	1.56	3.12	12.5	6.25	6.25	12.5	6.25	12.5
	899	3.12	1.56	1.56	12.5†	6.25	6.25	12.5†	12.5	6.25
	703	1.56	0.78	3.12	12.5	6.25	6.25	12.5	6.25	6.25
E. coli	483	6.25	3.12	6.25	6.25	6.25	12.5	12.5	12.5	12.5
	685	1.56	1.56	1.56	12.5	6.25	6.25	12.5	6.25	6.25
	863	6.25	3.12	3.12	12.5	12.5	12.5	12.5	12.5	12.5
	410	6.25	3.12	3.12	12.5	6.25	6.25	12.5	12.5	12.5
	869	6.25	6.25	6.25	12.5	12.5	12.5	12.5	12.5	12.5
	472	1.56	1.56	3.12	12.5	3.12	3.12	12.5	6.25	6.25

*MH = Mueller-Hinton broth; TSB = trypticase soy broth; TPO_4 = tryptose phosphate broth.

†Skipped tube phenomenon exhibited. No visible growth in tube containing 3.12 µg/ml, growth in tube with 6.25 µg/ml, and no growth in tube containing 12.5 µg/ml. MIC was taken to be the higher concentration.

TABLE 2

Effect of Inoculum Size of *Klebsiella* and *E. coli* Strains on Three Different Media Tested With 30-µg Discs of Cephalothin

		Diameter of inhibition zone (mm)						
	Strain	At 10^{-1} dilution			At 10^{-3} dilution			MIC
Organism	number	MH*	TSA	RBA	MH	TSA	RBA	(µg/ml)
Klebsiella	577	16.5	17.9	18.5	22.3	23.2	22.0	6.25
	796	17.5	16.6	18.2	22.3	23.2	23.3	6.25
	714	16.3	16.2	16.4	22.7	21.6	20.6	6.25
	899	17.9	18.6	19.0	24.1	23.6	24.6	12.5
	703	16.7	17.5	16.9	22.8	23.6	23.1	6.25
E. coli	483	16.9	14.0†	14.4	20.2	19.2	20.3	12.5
	685	18.7	14.7†	15.9	23.9	23.8	23.8	6.25
	863	12.5	R‡	R‡	19.8	19.5	18.7	12.5
	410	17.4	R‡	R‡	20.9	21.2	20.7	12.5
	869	15.6	R‡	11.0	19.7	18.8	19.3	12.5
	472	18.0	14.5	13.7	21.7	21.5	21.8	6.25

*MH = Mueller-Hinton agar; TSA = trypticase soy agar; RBA = trypticase soy agar with 5% rabbit blood. †Small colonies in zone. ‡R = Resistant (zone diameter <10 mm).

ble 2). In addition, with the 10^{-3} dilution, no differences were noted between zone diameters on the three media used in the disc test (Table 2).

Discussion

The reported sensitivity of gram-negative bacilli to cephalothin has ranged from 3.12 to 25 μg/ml.[2,12] A clinically useful level of sensitivity is one which is readily attainable in serum and body fluids with the usually recommended doses of the drug. This level is approximately 10.0 to 12.5 μg/ml one-half hour after a 0.5-gm intramuscular dose,[2,6,13] although urinary concentrations of the drug are considerably higher than those attainable in the serum.[6] With 12.5 μg/ml or less as the criterion for sensitivity in this study, 80% of *Klebsiella* strains were sensitive, but all of the *Enterobacter* strains were resistant. These findings are consistent with those of other studies.[3-5] This marked generic difference has been ascribed to cephalosporinase production by *Enterobacter*.[3] With this same criterion, 74% of the *E. coli* strains tested were sensitive.

Although the manufacturer of the antibiotic states that any zone of inhibition around the cephalothin disc indicates susceptibility of the organism and that the zone will probably be at least nine to 10 mm in diameter,[14] our data demonstrate that, for the three groups of organisms studied, this statement is not consistent with results of parallel tube dilution tests. Bauer and associates, as quoted by Lorian,[15] defined 16 mm or greater as the tentative standard zone size for indication of sensitivity of microorganisms to cephalothins. Application of this criterion to these results would have classified 94% of the *Klebsiella* strains, 89% of the *E. coli* strains, and 16% of the *Enterobacter* strains as being sensitive, and all strains considered to be resistant by the disc diffusion method were also resistant by the tube dilution technique. Increasing the minimal zone diameter for definition of sensitivity to 20 mm in the case of *Klebsiella* (Figure 2) would have decreased the number of strains falsely judged to be sensitive by the disc diffusion method from 11 (14%) to five (6%).

On the other hand, by using this higher criterion of sensitivity, one strain considered to be sensitive by the tube dilution method would have become resistant in the disc diffusion test.

A similar 20-mm criterion for *Enterobacter* would have eliminated all the false-positive results (strains sensitive by the disc diffusion method but resistant by the tube dilution method) and would have given no false-negative results (strains sensitive by the tube dilution method but resistant by the disc diffusion method). In the case of *E. coli* (Figure 3), 11 strains (15%) were considered to be sensitive by the disc diffusion method and resistant by the tube dilution method. Increasing the minimal zone diameter for definition of sensitivity to 18 mm would have decreased this number of false-positive results to eight strains (10%); however, five strains sensitive in the tube dilution test would have become resistant in the disc diffusion test.

There thus appears to be no useful agreement between the disc diffusion and tube dilution methods for testing sensitivity of *Klebsiella* spp. and *E. coli* to cephalothin, because use of the recommended 16-mm zone of inhibition yields a significant number of false-positive interpretations and the use of a larger zone diameter yields a significant number of false-negative interpretations. With *Enterobacter* spp., false-positive results were eliminated by increasing the minimal zone size to 20 mm.

Agreement between the tube dilution and disc diffusion tests was not changed by altering the medium used in either test. Although the disc diffusion method is widely used and is simpler to perform than the tube dilution method, the results obtained by the former method may be affected by the depth of the agar,[16] method of inoculation,[17] prediffusion time,[18] variation in amount of antibiotic present in individual discs,[10] and molecular weight of the antibiotic. The tube dilution technique remains the more reliable and more accurate method, provided it is properly controlled,[9] and is therefore the criterion against which the disc diffusion method should be evaluated. This study strongly suggests that, with patients in whom *E. coli*, *Klebsiella* spp. or *Enterobacter* spp. are of particular clinical significance, sensitivity tests should be performed by the tube dilution method.

Acknowledgment

The authors thank Mr. Norris O. Robinson and Mrs. G. Woods for their technical assistance and Dr. Lila R. Elveback, Section on Medical Statistics, Epidemiology and Population Genetics, Mayo Clinic, for review of the data and conclusions presented in this report.

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His Nganga* Failed

Mbavimbvi:† a MuZezuru aged forty, admitted with unresolved pneumonia. He had been suffering with chest pains and a cough for a month prior to admission to hospital. His nephew had consulted a diviner who said that Mbavimbvi had not returned a cow to his mother before her death. Her spirit was now a ngozi (an aggrieved spirit) and had caused the illness. By this time the patient was in hospital, but the nephew replaced the cow and eventually Mbavimbvi recovered and left hospital.‡

---

*Nganga—Southern Rhodesian witch doctor
†Mbavimbvi was admitted to a Southern Rhodesian hospital after his nganga failed to cure him.
‡Michael Gelfand: Witch Doctor, 1965.

A summer's observation on the highways enabled us to determine the average motorist's average speed: 10 miles over the limit.—Changing Times

Physician's Diary

Dr. Jerome T. Grismer, Director of the Cardiopulmonary Department of Mount Sinai Hospital, is the new president of the Greater Hennepin Division of the Minnesota Heart Association.

* * *

Dr. Carl Lund was honored by Fergus Falls recently on occasion of his twenty-five years of service as the medical examiner for Selective Service in that community.

* * *

Dr. Henry E. Nelson of Crookston has been honored by that community on occasion of his fifty-five years as County Coroner and fifty years as general practitioner, and **Dr. Joseph Bloom** after serving Silver Bay area for more than thirty-five years in the practice of medicine has closed his office.

* * *

Dr. Timothy Eugene Nealy has been elected to active membership in the American Academy of General Practice, and **Dr. Delmar R. Gillespie,** president-elect of the Minnesota State Medical Association, together with his wife, has been named host for a delegation of medical leaders on a 22-day goodwill people-to-people inspection mission throughout Europe and the Soviet Union.

* * *

Dr. Viktor Wilson, Rochester-Olmsted County Public Health Officer, recently was honored on occasion of his retirement.

* * *

New Locations: Doctors Thomas T. Myers, III, Charles R. Peterson, Wilfred A. Corson, and **Richard C. Hughes** have joined the St. Louis Park Medical Center. . . . **Dr. Thomas F. Gilles** is practicing medicine in Fairfax. . . . **Dr. Brandon Adams** has joined the staff of the Fridley Medical Center. . . **Dr. Narcis P. Cabot** has joined the practice of **Dr. S. T. Normann** in Waseca. . . . **Dr. Neal R. Olson** has joined the Olmsted Medical Group in Rochester. . . . **Doctors Jon Fredlund** and **Daniel Baker** recently became associated with the Mork Clinic in Anoka. . . . **Dr. John Verby,** a member of the Olmsted Medical Group, has resigned to accept a position as associate professor of a newly created department of family medicine and community health at the University of Minnesota Medical School.

* * *

Dr. L. Emerson Ward, consultant with the Mayo Clinic, was named president of the American Rheumatism Association at the organization's annual meeting in Seattle.

* * *

Dr. Ralph B. Johnson of Lanesboro, was honored by that community on occasion of his 37 years in the practice of medicine.

* * *

The September issue of **Minnesota Medicine** stated that **Dr. Ben M. Tuma** had moved from Montgomery to join the Alexandria Clinic. This was in error. Dr. Tuma is associated with the Faribault Clinic in Faribault and not the Alexandria Clinic.

* * *

Two Minnesota doctors, graduates of the University of Minnesota medical school, **Dr. Walter Halloran** of Jackson, and **Dr. Anderson C. Hilding** of Duluth, were presented the Harold S. Diehl Award last October for outstanding contributions to the medical profession.

Dr. Noel Van Ness, a Mayo Graduate school resident in orthopedic surgery, in in Tandala in the Congo, practicing in a 125-bed hospital. He will return to the Clinic next year.

* * *

Dr. George Hallenbeck, world-famed Mayo Clinic surgeon who twice operated on President Lyndon Johnson, has resigned from the Clinic to join former Clinic open heart surgeon pioneer, **Dr. John Kirklin,** at the University of Alabama Medical Center in Birmingham. **Dr. Robert Wallace** has been named chairman of the sections of surgery, succeeding **Dr. Hallenbeck.**

* * *

Dr. Richard E. Olson of Chaska has been elected to active membership in the American Academy of General Practice.

* * *

Dr. Edward S. Judd, Mayo Clinic general surgeon, has been elected second vice president of the American College of Surgeons.

* * *

Dr. Paul Lipscomb, orthopedic surgeon at the Mayo Clinic since 1943, has resigned his Clinic post, to become professor and chairman of the Department of Orthopedic Surgery at the University of California's new medical school at Davis.

* * *

Dr. Alvin S. Zelickson, Minneapolis, has been elected to the Board of Directors of the Society for Investigative Dermatology. Dr. Zelickson is Associate Professor of Dermatology at the University of Minnesota Medical School.

* * *

Dr. Walter F. Larrabee, Jr. has been named medical director at the Willmar State Hospital.

* * *

The following surgeons were inducted as new Fellows of the American College of Surgeons in October: **Dr. Clifford M. Phibbs, Jr.** of Bloomington; **Dr. William G. Merrick** of Duluth; **Dr. Cecil L. Provence** of Waconia; **Doctors Donald A. Bolt, Henry Buchwald, Victor A. Gilbertsen, David F. Hickok, Colin Markland, John J. Sciarra, Henry Sosin** and **Paul B. Stewart** of Minneapolis; **Dr. Russell L. Edwin** of North Mankato and **Doctors Barclay M. Cram, Robert S. Flom, James W. LaFave, Charles H. Manlove, Jr., Michael P. Sperl, Jr., Wayne W. Thompson** and **Neil M. Trotman** of St. Paul.

* * *

Dr. A. B. Rosenfield, State Health Department, has been awarded the Albert Justus Chesley Award for distinguished service in public health in Minnesota by the Minnesota Public Health Association.

* * *

Dr. Carl Simison was honored recently by the community of Barnesville on occasion of thirty years of practice in that town.

* * *

Dr. Earl Elkins, senior consultant of physical medicine and rehabilitation at the Mayo Clinic, recently received a recognition award from the Rochester Chapter of the National Paraplegic Foundation. Dr. Elkins received the award for his work in paraplegia in Rochester.

"The inconvenience of a cold"

For a cold, NTz® Nasal Spray provides rapid relief of nasal symptoms. Relief starts with the first spray which opens the inferior part of the common meatus. A second spray, a few minutes later, will shrink the turbinates to help provide sinus drainage and ventilation. Dosage may be repeated every three or four hours as needed, for temporary relief of symptoms. NTz is well tolerated but overdosage should be avoided.

As a sinusitis deterrent, NTz Nasal Spray can be used to keep the nasal passages open during a cold to help prevent development of acute sinusitis—or to help prevent the acute condition from becoming chronic.

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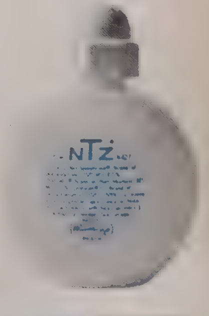

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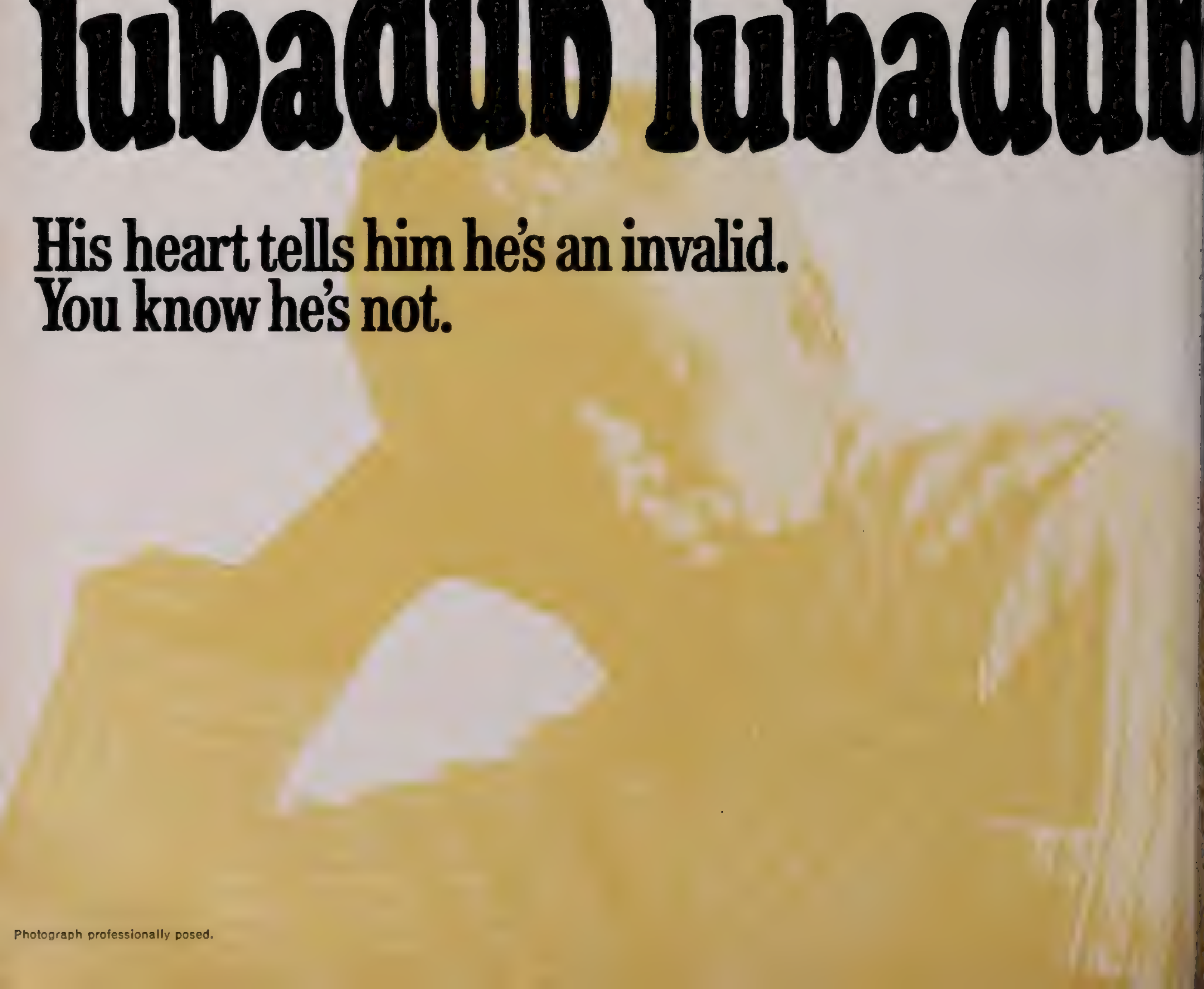
lubadub lubadub
His heart tells him he's an invalid.
You know he's not.

Photograph professionally posed.

badubdub lubad

nxiety is expected in the cardiovascular patient. little may even be desirable.

ut when anxiety is exaggerated . . . when it nterferes with sleep . . . when it aggravates ardiovascular symptoms, your help may e needed.

aturally, you'll want to reassure the patient.

nd perhaps prescribe Equanil (meprobamate) s adjunctive therapy. It helps relieve anxiety nd tension specifically, yet gently.

lmost 15 years' use has shown that Equanil s usually well tolerated as well as effective. ide effects are generally limited to transient rowsiness; serious, therapy-interrupting ide effects are rare.

Contraindications: History of sensitivity to meprobamate.

Important Precautions: Carefully supervise dose and amounts prescribed, especially for patients prone to overdose themselves. Excessive prolonged use has been reported to result in dependence or habituation in susceptible persons, as alcoholics, ex-addicts, and other severe psychoneurotics. After prolonged excessive dosage, reduce dosage gradually to avoid possibly severe withdrawal reactions. Abrupt discontinuance of excessive doses has sometimes resulted in epileptiform seizures.

Warn patients of possible reduced alcohol tolerance, with resultant slowing of reaction time and impairment of judgment and coordination.

Reduce dose if drowsiness, ataxia or visual disturbance occurs; if persistent, patients should not operate vehicles or dangerous machinery.

Side Effects include drowsiness, usually transient; if persistent and associated with ataxia, usually responds to dose reduction; occasionally concomitant CNS stimulants (amphetamine, mephentermine sulfate) are desirable. Allergic or idiosyncratic reactions are rare, but such reactions, sometimes severe, can develop in patients receiving only 1 to 4 doses who have had no previous contact with meprobamate. Previous history of allergy may or may not be related to incidence of reactions. Mild reactions are characterized by itchy urticarial or erythematous maculopapular rash, generalized or confined to groin. Acute nonthrombocytopenic purpura with cutaneous petechiae, ecchymoses, peripheral edema and fever have been reported. One fatal case of bullous dermatitis following intermittent use of meprobamate with prednisolone has been reported. If allergic reaction occurs, meprobamate should be stopped and not reinstituted. Severe reactions, observed very rarely, include angioneurotic edema, bronchial spasms, fever, fainting spells, hypotensive crises (1 fatal case), anaphylaxis, stomatitis and proctitis (1 case) and hyperthermia. Treat symptomatically as with epinephrine, antihistamine and possibly hydrocortisone. Aplastic anemia (1 fatal case), thrombocytopenic purpura, agranulocytosis and hemolytic anemia have occurred rarely, almost always in presence of known toxic agents. A few cases of leukopenia, usually transient, have been reported on continuous administration.

Meprobamate may sometimes precipitate grand mal attacks in patients susceptible to both grand and petit mal. Extremely large doses can produce rhythmic fast activity in the cortical pattern. Impairment of accommodation and visual acuity has been reported rarely. After excessive dosage for weeks or months, withdraw gradually (1 or 2 weeks) to avoid recurrence of pretreatment symptoms (insomnia, severe anxiety, anorexia). Abrupt discontinuance of excessive doses has sometimes resulted in vomiting, ataxia, tremors, muscle twitching and epileptiform seizures. Prescribe very cautiously and in small amounts for patients with suicidal tendencies. Suicidal attempts have resulted in coma, shock, vasomotor and respiratory collapse and anuria. Excessive doses have resulted in prompt sleep; reduction of blood pressure, pulse and respiratory rates to basal levels; and occasionally hyperventilation. Treat with immediate gastric lavage and appropriate symptomatic therapy. (CNS stimulants and pressor amines as indicated.) Doses above 2400 mg./day are not recommended.

Composition: Tablets, 200 mg. and 400 mg. meprobamate. Coated Tablets, WYSEALS® EQUANIL (meprobamate) 400 mg. (All tablets also available in REDIPAK® [strip pack], Wyeth.) Continuous-Release Capsules, EQUANIL L-A (meprobamate) 400 mg.

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Novahistine® Singlet decongestant-analgesic

(Each tablet contains: phenylephrine hydrochloride, 40 mg.; chlorpheniramine maleate, 8 mg.; acetaminophen, 500 mg.)

DOW

**Mark Waters was a chain smoker.
Wonder who'll get his office?**

Too bad about Mark. Kept hearing the same thing everyone does about lung cancer. But, like so many people, he kept right on smoking cigarettes. Must have thought, "been smoking all my life... what good'll it do to stop now?" Fact is, once you've stopped smoking, no matter how long you've smoked, the body begins to reverse the damage done by cigarettes, provided cancer or emphysema have not developed. Next time you reach for a cigarette, think of Mark. Then think of your office —and your home.

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Clinical Path Conference

Acute Abdominal Emergency after Gastrectomy

Robert L. Strom, M.D.:*

Case Report

A 59-year-old chronic alcoholic male was admitted to Hennepin County General Hospital on December 27, 1967, because of a long history of epigastric pain and a pre-pyloric gastric ulcer demonstrated by x-ray. He had refrained from drinking alcoholic beverages for three years; however, the pain had recently become constant and was no longer relieved by food or antacids. There was no bleeding history.

The patient had mild, mature onset diabetes mellitus which was well controlled with Orinase. His physical examination was essentially normal except for obesity and a liver which was palpable 4 cm. below the right costal margin.

Gastric x-rays and gastroscopy revealed a pre-pyloric gastric ulcer and a small hiatus hernia. Preoperative studies included a 12-hour gastric specimen of 350 ml. containing 54 mEq of free acid per liter. The gastric fluid pH was less than 4.5. After four weeks of intensive medical management failed to improve the symptoms or the x-ray picture, surgical management was felt advisable.

Exploratory

On February 7, 1968, the patient underwent exploration through a bilateral subcostal incision. Operative findings included gallstones, diverticulosis of the colon, duodenal and antral scarring and a hiatus hernia. A vagotomy was performed; definite anterior and posterior vagal trunks were identified and confirmed by frozen sections. The crurae of the diaphragm were closed behind the esophagus and the gastroesophageal angle was reconstructed by suturing the fundus of the stomach to the esophagus anteriorly and posteriorly. A 50% gastrectomy was performed with a retrocolic Billroth II type reconstruction and a short afferent loop. The rent in the mesocolon through which the loop of jejunum passed was tacked to the jejunum with interrupted sutures. A cholecystectomy was performed and the abdomen was closed. Anatomic function was demonstrated by gastrointestinal x-rays and is illustrated in Figure 1.

Discharged

On the second postoperative day the patient developed auricular fibrillation with tachycardia and hypotension which reverted to sinus rhythm with aramine, digitalis and quinidine therapy. Although urine output remained within normal limits, the BUN was elevated one week postoperatively to 76 mg.% and the creatinine rose to 4.8 mg.%. Dehydration secondary to renal tubular injury was suggested by a renology consultation. The patient responded well to rehydration, and urine output ranged from 2500 ml. to 5500 ml. per day. He was discharged on March 13, 1968, on Diabinase and ferrous gluconate.

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*Associate Pathologist, Hennepin County General Hospital.

Readmitted

The patient did well until June 14, 1968, when he was readmitted to the surgical service after awakening with severe epigastric pain. He ate breakfast and then came to the Emergency Room where he was noted to be pale and clammy. On admission at 11 a.m. his blood pressure was 60 systolic, his pulse 120 per minute and thready, his temperature 96.4° F. The abdomen was distended, with tenderness most marked in the upper quadrants. Bowel sounds were hypoactive and then became absent within one hour. Peripheral pulses were present and no abdominal masses were palpable. A chest x-ray was normal. A flat and upright film of the abdomen showed a vague collection of fluid centrally which was considered both intraluminal and extraluminal (Figure 2).

Laboratory studies included a hemoglobin of 15.6 gm.%, a white blood cell count of 28,500 per cu. mm., and the following serum electrolytes: sodium 137 mEq/L, potassium 4.0 mEq/L, chloride 101 mEq/L, CO_2 16 mEq/L. Total serum proteins were 7.7 gm.% with albumin 4.2 gm.%. A serum calcium was 10.8 mg.% and the SGOT was 70 units. A BUN was 25 mg.% and a blood glucose measured 340 mg.%. Liver function studies included a total bilirubin of 1.1 mg.% and alkaline phosphatase of 12 KA units. The plasma amylase was 1300 Somogyi units.

A short time after admission the patient stopped breathing and was intubated and placed on assisted respiration. Little or no urine output was noted after admission in spite of fluid,

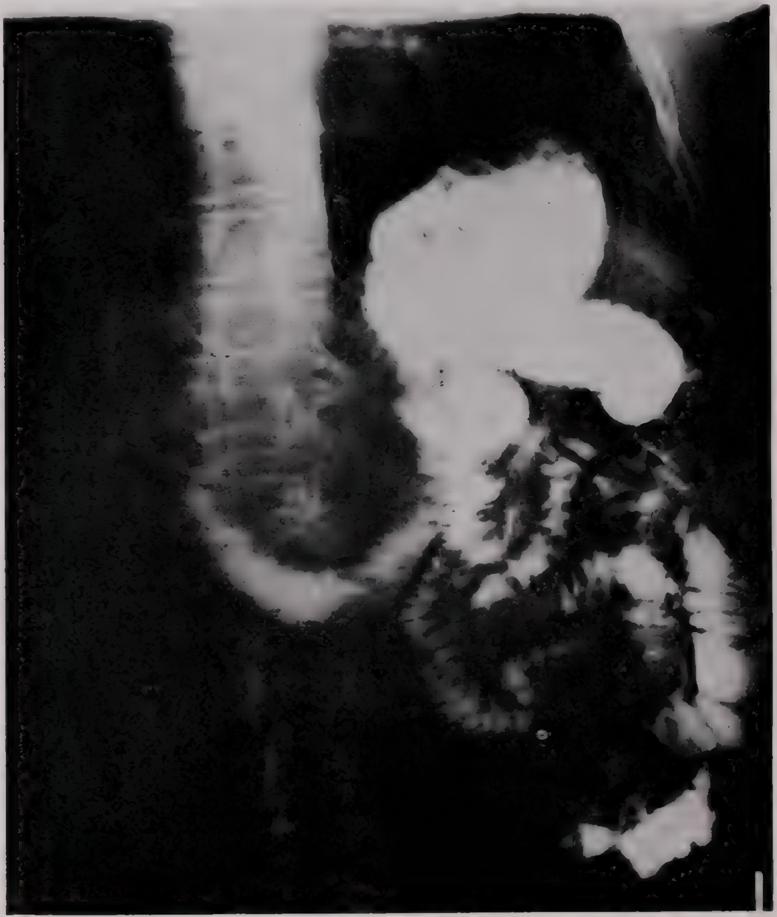

Fig. 1—Gastrointestinal x-rays during the postoperative period revealing functional retrocolic anastomosis and Billroth II gastrectomy.

plasma and blood infusions. His blood pressure was unstable with peaks of 120 mm. Hg. systolic and valleys to 80 to 90 systolic. He remained essentially anuric. Early the following day increasing abdominal distention in the presence of nasogastric suction necessitated tracheotomy and peritoneal drainage with a dialysis cannula. The peritoneal fluid was blood-tinged with an amylase of 1,050 units, and gram-negative rods were present on gram smear. Enterobacter species was cultured from the peritoneal fluid. The patient suffered a cardiac arrest and after temporary resuscitation was pronounced dead at 11 a. m. on June 15, 1968. An autopsy was performed.

Discussion

William G. Gamble, M.D.:*

We are presented with a case of a 59-year-old male, a chronic alcoholic, who succumbed of an acute abdominal process within 24 hours after admission to the hospital. Interestingly enough, this occurred four months after vagotomy and hemigastrectomy for presumed benign peptic ulcer disease.

I will begin my discussion by considering the terminal illness and reflect on the history of his preceding hospitalization, only as it is pertinently related.

I would like to discuss the differential diagnosis with specific regard to the markedly and consistently elevated serum and peritoneal fluid amylase levels. These data need to be explained in reference to the acute illness. I am not implying that one can disregard the other historical and clinical data, for these need to be closely correlated.

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*Staff Surgeon, St. Louis Park Medical Center and Attending Surgeon, Hennepin County General Hospital.

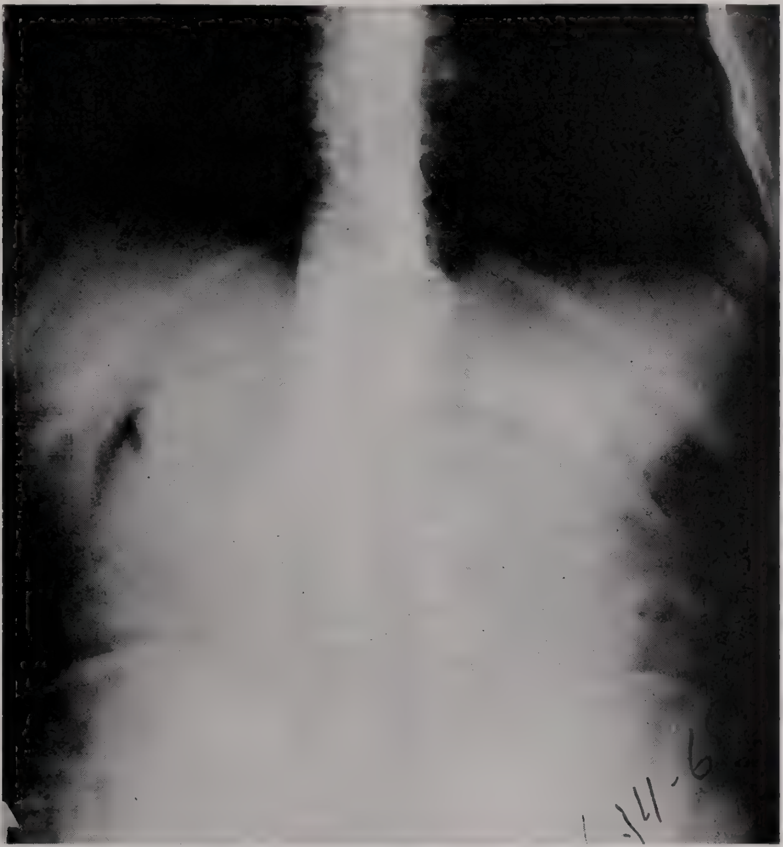


Fig. 2—Flat plate of abdomen with evidence of abdominal fluid and gas in colon.

The serum amylase determination probably represents the single most important laboratory aid in the diagnosis of acute edematous pancreatitis and acute hemorrhagic pancreatitis. Although serum amylase elevations are rather consistent in acute pancreatitis, the value of this test is limited by the fact that elevations may often occur in a variety of other acute intra-abdominal disorders. Significant elevations may also be observed in parotitis, acute renal insufficiency, and subsequent to the administration of opiates. Acute abdominal conditions, other than pancreatitis, associated with elevations in the serum amylase are pancreatic pseudocysts, acute cholecystitis, impacted ampullary calculus, perforated ulcer, strangulated intestinal obstruction, mesenteric thrombosis and acute afferent loop obstruction.

Hemorrhagic Pancreatitis

Acute hemorrhagic pancreatitis immediately comes to mind in this case because of the marked elevation of serum amylase and the presence of bloody peritoneal fluid, rich in amylase. The rapid demise of this patient with associated profound shock is compatible with fulminating acute hemorrhagic pancreatitis.

Although the specific cause of this disease is unknown, it is most commonly related to chronic alcoholism and biliary tract disease. One wonders why this patient did not develop this disease earlier since we are told he was a confirmed chronic alcoholic. If we are to believe the history, however, he had abstained from drinking alcoholic beverages for several years. Biliary tract disease would not seem to be related, because an incidental cholecystectomy was performed at his previous surgery and no mention was made of common bile duct pathology.

Postoperative pancreatitis is another consideration since this most often occurs following gastric or biliary surgery. This condition is thought to be due to operative injury of the duct of Santorini, especially in instances where this duct represents the major source of pancreatic drainage. Leakage of pancreatic secretions from an injured duct has also been implicated. But I believe this diagnosis can be ruled out on the basis of the time interval involved. This condition characteristically occurs in the early postoperative period; in fact, this feature serves to distinguish it from other postoperative complications such as leakage from the duodenal stump.

Pancreatic Pseudocyst

Pseudocyst of the pancreas is usually associated with persistent elevations of the serum amylase. This condition is a complication of idiopathic or traumatic pancreatitis and is preceded by clinical evidence of acute pancreatic disease. The absence of any prodromal illness in this case, I believe, effectively rules out this diagnosis.

Perforated Ulcer

Perforated peptic ulcer (usually duodenal) may be associated with marked elevations of serum amylase. This is thought to be due to leakage of pancreatic enzymes with rapid absorption by the inflamed peritoneal surfaces. In this case, the ulcer would have had to be of the marginal variety. Marginal ulcer occurring two months after definitive gastric surgery is distinctly uncommon in the absence of hypersecretion secondary to non-beta islet cell lesions of the pancreas (Zollinger-Ellison syndrome). The preoperative gastric secretory studies do not indicate hypersecretion of the magnitude seen in this condition. One also would not expect the peritoneal fluid to be blood-tinged, as it was in this case. The peritoneal fluid associated with perforations of the upper gastrointestinal tract is cloudy serous fluid and not serosanguineous.

Ampullary Calculus

High levels of serum amylase may be observed in patients with calculus obstruction of the common bile duct. This may or may not be associated with pancreatitis. It is explained by the "common channel theory" with regurgitation of pancreatic enzymes into the blood stream secondary to obstruction of the duct of Wirsung. Patients with this condition demonstrate chemical and/or clinical hyperbilirubinemia. One would also expect that there would have been prodromal symptoms.

Mesenteric Vascular Occlusion

Some of the highest serum and peritoneal fluid amylase values are seen in patients with infarction of the proximal small bowel secondary to transudation of pancreatic enzymes through the injured bowel wall.

Mesenteric vascular occlusion may result from thrombosis of the superior mesenteric artery secondary to atherosclerosis. Patients with this condition are usually older than our patient and generally have evidence of atherosclerosis elsewhere. Embolization involving the superior mesenteric artery may also produce this lesion, which usually occurs in patients with arteriosclerotic or valvular heart disease and cardiac arrhythmias. Although we are told that our patient developed atrial fibrillation during his previous postoperative course, he converted to sinus rhythm and did not revert to fibrillation.

Mesenteric venous thrombosis, either idiopathic or secondary to other intra-abdominal pathology, may also be implicated. Idiopathic mesenteric venous thrombosis is most often associated with evidence of other thromboembolic phenomena, but such history is absent in this case.

Finally, the mode of onset and the clinical course of patients with this condition are more gradual. Demise does not usually occur for twenty-four to forty-eight hours. Patients do not become moribund within a few hours, as this patient did.

Strangulation Obstruction

Strangulation obstruction, especially that involving the proximal small bowel, may result in marked elevations of serum and peritoneal fluid enzyme levels. The mechanism again is transudation of these enzymes through the injured bowel wall.

Strangulation obstruction is usually secondary to volvulus or internal herniation of the small bowel. Volvulus may occur around any fixed point within the peritoneal cavity, particularly in patients who have adhesions from previous abdominal surgery. Internal hernias may occur after gastric surgery and are particularly prone to follow anticolic anastomoses. The small bowel may herniate from left to right or right to left behind a long afferent loop. This may also occur posterior to the anastomosis following a retrocolic gastrojejunostomy, particularly if the gastric remnant is brought well below the mesocolon to allow space for herniation.

In this specific case we are told that the anastomosis was performed above the mesocolon and that the loop of jejunum used was sutured to the defect in the mesocolon. If the anastomosis was not done immediately at the ligament of Treitz with a maximally short afferent loop, there could have been a space behind the afferent and efferent loops to allow for internal herniation. An internal herniation of this type could certainly explain the entire clinical picture in this case and remains an excellent possibility. Although I cannot completely rule this out, I favor another diagnosis.

Afferent Loop Obstruction

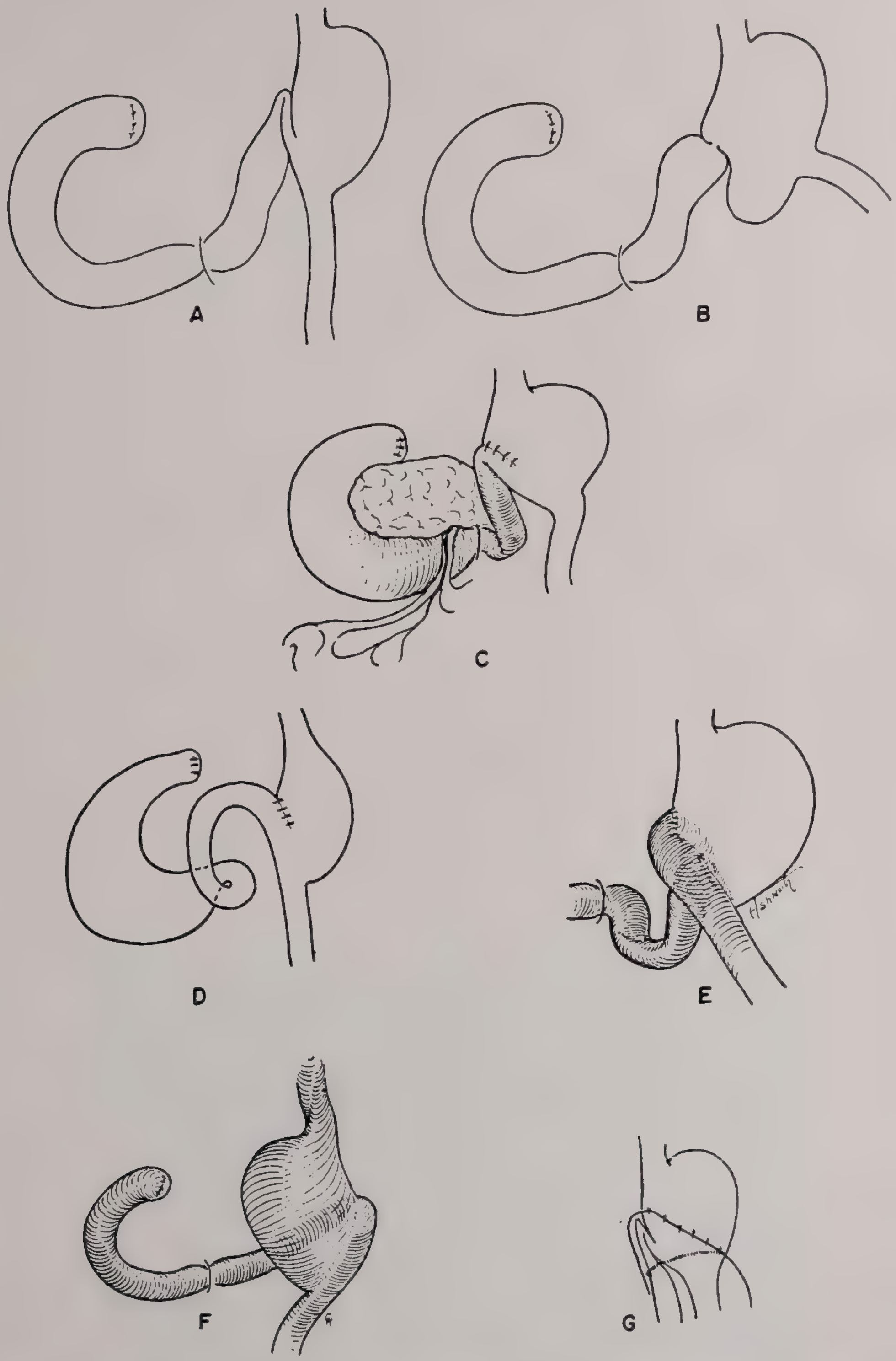
The afferent loop syndrome actually consists of a group of conditions involving malfunction of the afferent loop which are frequently not clearly separated from the numerous conditions considered under the term "postgastrectomy syndrome." Afferent loop problems have been recognized since the first gastroenterostomy was performed by Wölfler in 1881. Just four years later, in 1885, Von Hacker devised the retrocolic anastomosis in hope of circumventing some of the problems that occurred with redundant anticolic afferent loops.

The major pathologic feature of the afferent loop syndrome is obstruction or stasis which may be produced by a number of mechanisms, such as kinking at the anastomosis due to tension, volvulus of a long anticolic loop, compression of an anticolic loop by colon or omentum, and mesocolic obstruction of a retrocolic loop brought through the mesocolon. Some of the mechanisms are illustrated in Figure 3.

The afferent loop syndrome may be acute or chronic, depending on the degree of obstruction. The chronic form is seen with partial obstruction and results in symptoms of fullness, right upper quadrant pain and, most characteristically, bilious vomiting fifteen to thirty minutes following meals. The acute form, which may occur immediately postoperatively or later in the postoperative course, is due to acute afferent loop obstruction and is essentially a closed loop obstruction. It is this form that I would like to discuss further since I believe it may well be pertinent.

The mechanism of afferent loop obstruction in this case would most likely be due to mesocolic compression of the afferent loop. I presume that fixation of the gastroesophagel junction combined with 50-percent gastric resection prevented infracolic placement of the anastomosis in this obese individual. This mechanism has been implicated in similar cases and has occurred at approximately this same postoperative time interval. In fact, an almost identical case was reported from this institution in 1958 by Thal and Perry.[4] The history in this case is compatible with such a condition, particularly the fact that the patient's pain was present on awakening and was not post-cibal. It is believed that the afferent loop may become obstructed due to positional changes; in fact some patients with a less acute form of this condition find that they can avert symptoms by sleeping in various positions, usually on the left side. It would be important to know if the patient vomited, and if so, whether or not the emesis contained bile. It would also be important to know if the nasogastric tube returned bile-stained contents. The abdominal distention and tenderness localized in the upper quadrants would be compatible with this diagnosis. The x-rays which demonstrate a central fluid density and absence of bowel gas are absolutely characteristic of this condition.

The marked elevations of serum and peritoneal fluid amylase in this condition are typical, and there are two possible explanations for this. The



(Figure appeared on page 112 of Gastric Surgery by M. E. Steinberg published by Appleton-Century-Crofts of New York City and published herein with permission.)

pressure in the obstructed loop may have exceeded the secretory pressure in the pancreas; simple obstruction of the pancreatic duct may produce extreme elevations in serum amylase in the complete absence of pancreatitis. This has been demonstrated in the experimental animal and the human.[2,3] Secondly, pancreatic enzymes may have entered the peritoneal cavity by crossing the abnormally permeable gangrenous duodenal wall; the serosanguinous character of the peritoneal fluid, rich in amylase, would be considered typical.

In summary, the serum amylase concentration may prove to be a helpful adjunct in the clinical evaluation of patients with acute abdominal disease. Although elevations of the serum amylase in patients with abdominal pain generally imply a degree of pancreatitis, this may not always be the case. Blind reliance on this laboratory value may prove fatal. A recent study showed that the serum amylase level tended to be inversely related to the severity of pancreatic disease.[1] In fact, when the amylase level was over 1,000 Somogyi units there was usually a surgically correctable lesion. Interpretation of these laboratory data in the light of the total clinical picture will serve to select some cases with surgically remediable lesions.

Furthermore, I believe that the pancreas might well have been grossly and histologically normal at postmortem examination.

Final Clinical Diagnoses:

1. Acute obstruction of the afferent loop with gangrene and secondary massive generalized peritonitis
2. Possible strangulation obstruction secondary to internal herniation of the small bowel
3. Probable gram-negative septicemic shock

Pathology

Doctor Strom:

On postmortem examination, the major findings were limited to the abdomen. Approximately 800 cc. of bloody, foul-smelling fluid was present. The greater omentum was adherent to strangulated gas-filled loops of small bowel and colon.

A Billroth II type anastomosis was present in the left upper quadrant,

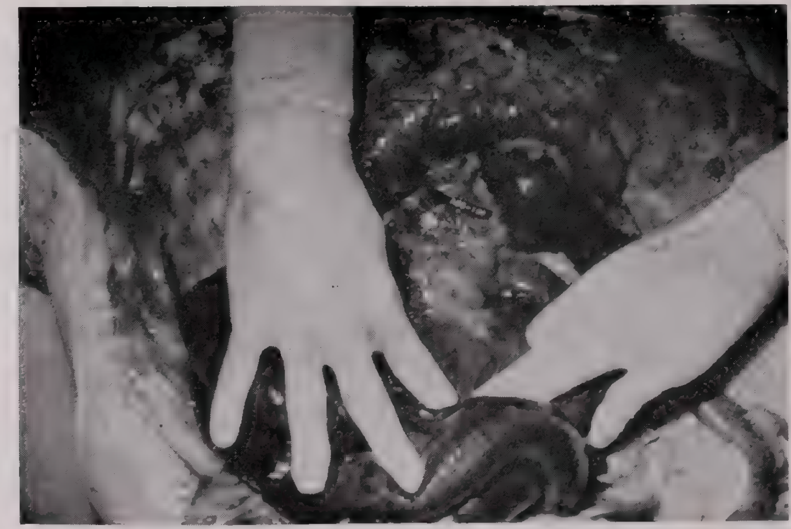


Fig. 4—The proximal loop of the anastomosis acting as an obstructing band overlying the body of the pancreas and occluding the root of the mesentery and superior mesenteric artery.

and the gastrojejunostomy was patent. The transverse mesocolon was securely in place around the proximal and distal loop of the anastomosis, and 500 cc. of clotted whole blood was present in the stomach. There was no evidence of peptic ulceration.

The most notable abdominal finding was a herniation of the distal loop of the anastomosis above the ligament of Treitz and under the transverse mesocolon. The proximal loop of the anastomosis then acted as an obstructing band overlying the body of the pancreas and occluding the root of the mesentery and superior mesenteric artery (Figure 4). The entire small bowel, right colon and transverse colon were involved in a process of hemorrhagic infarction and strangulation consistent with the distribution of the superior mesenteric artery (Figure 5). The loops of small and large bowel were blood-filled, and the devitalized bowel made the largest contribution to the plasma amylase level.

The pancreatic findings were of particular interest. The head of the pancreas was edematous and showed bilious discoloration. Focal hemorrhagic necrosis of the body of the pancreas was present under the occluded superior mesenteric artery although the tail of the pancreas was spared and changes of acute pancreatitis were minimal. The duodenal loop was dilated and showed some violet discoloration; the duodenal stump was adherent to the undersurface of the liver. There appeared to be some element of an afferent loop obstruction present.

Considerable pulmonary atelectasis and edema were present as well as bilateral hydrothorax. Focal infarction of the hepatic tissue and mild fatty metamorphosis were notable on microscopic examination of the liver. The renal cortices were pale and showed evidence of acute evolving tubular necrosis.

Serum Amylase Levels

Burnett and Ness[5] studied serum amylase levels in a series of 350 patients admitted to the hospital with acute abdominal pain. There were twelve cases of acute pancreatitis: an incidence of 3.4%; the serum amylase levels in these 12 cases varied between 1200 to 6000 Somogyi units. Burnett and Ness felt that the serum amylase level was useful in differentiating acute

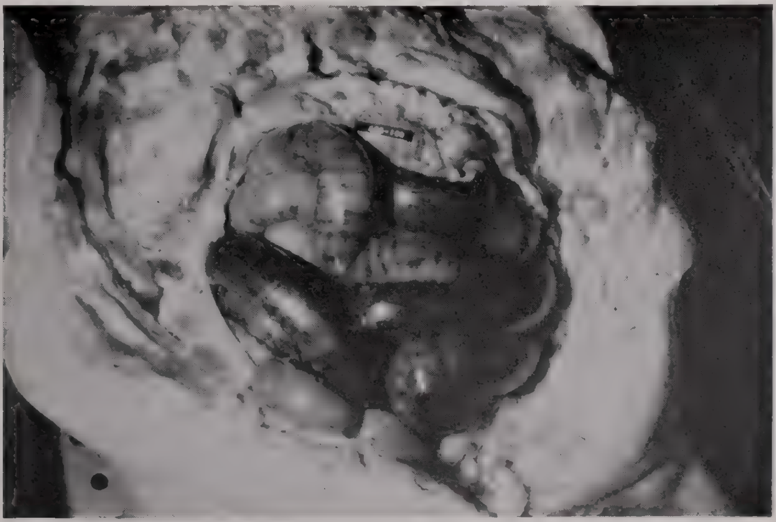


Fig. 5—Internal hernia and superior mesenteric artery thrombosis.

cholecystitis but not pathognomonic of acute pancreatitis, as high levels were also found in perforated peptic ulcer and intestinal obstruction.

A significant rise in serum amylase activity occurred in a number of cases of intestinal obstruction. In Burnett and Ness' series of 35 patients, using Somogyi's method, 19 patients were found whose values were above their normal range of 62 to 177 Somogyi units (mean 115 ± SD 33 Somogyi units). In these cases two serum amylase levels were very high: one, 1600 Somogyi units, and the other, 2000 Somogyi units. Both of these patients had extensive devitalization of small bowel accompanying the intestinal obstruction. It is postulated that the amylase of the intestinal content was absorbed by capillaries or lymphatics of the damaged bowel or from the peritoneum after seeping through the intestinal wall. The intestinal cells of the crypts of Lieberkuhn may also have contributed some desquamated amylase; amylase-producing bacteria have been cultured from fecal flora.

TABLE

Diagnosis	No. of Cases	Serum Amylase > 400 Units	Serum Amylase > 1000 Units
Acute pancreatic disease	14	14	13
Acute cholecystitis	23	2	0
Perforated peptic ulcer	31	8	2
Intestinal obstruction	35	3	2
Acute appendicitis	149	2	0
Miscellaneous	98	3	0
TOTAL	350	32	17

Burnett & Ness: Brit Med J. 2:770, 1955.

Hiatt[6] studied the mechanism of serum amylase elevation and noted that in simple mechanical obstruction in the dog, without strangulation, the serum amylase levels were not elevated. However, strangulation obstruction with necrosis of mucosa was followed by significant rises in plasma amylase values: rises which occurred in depancreatized dogs as well. He ascribed the elevations to absorption of enzymes seeping through the devitalized bowel wall into the peritoneum; the peritoneal fluids often had values for serum amylase above the plasma. These workers found no evidence of pancreatitis resulting from their maneuvers.

The mechanism of serum amylase elevation in acute interstitial and hemorrhagic pancreatitis is poorly understood. It has been found that serum amylase levels rise abruptly during acute episodes and fall sharply after 24 to 36 hours, with normal values being gradually reached in four to five days. All of us have had the experience of observing cases of acute hemorrhagic pancreatitis with normal serum amylase levels in spite of tubular necrosis and renal failure. Pancreatic duct obstruction is not uniformly present in cases of acute interstitial or hemorrhagic pancreatitis. The amount of pancreatic secretory mass appears to bear some relationship to serum amylase elevations particularly in cases of chronic pancreatitis.

Closed loop obstruction of the duodenum in the area where the pancreatic duct enters is a well-defined variety of pancreatitis which was studied by Pfeffer and his colleagues.[7] Our case today involved an afferent loop obstruction and a strangulation obstruction of the small bowel secondary to internal hernia.

Pathologic Diagnoses:

1. Strangulation obstruction of small bowel secondary

to internal herniation of small bowel after retrocolic gastrojejunostomy.

2. Afferent loop obstruction of the duodenum
3. Mechanical obstruction of the superior mesenteric artery by the proximal loop of the gastric anastomosis
4. Acute peritonitis
5. Renal tubular necrosis

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Dr. Donald Bell is an internist practicing in Minneapolis in the Medical Arts Building. A graduate of the University of Minnesota Medical School, Dr. Bell completed his postgraduate work at the Mayo Clinic in Rochester.

The cover picture "Lily Pad Fantasy" was taken by Dr. Bell in late afternoon as the sun was reflected on Camp Lake, which is located near Garrison, Minnesota.

An Open Mind

An open mind is all very well in its way, but it ought not to be so open that there is no keeping anything in or out of it. It should be capable of shutting its doors sometimes, or it may be found a little draughty.—Samuel Butler

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A wonderful discovery—psychoanalysis. Makes quite simple people feel they're complex.—S. N. Behrman

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What I mean is this—all good doctors must be primarily enthusiasts. They must have, like writers and painters, and priests, a sense of vocation—a deep-rooted, unsentimental desire to do good.—Noel Coward

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The American people never carry an umbrella. They prepare to walk in eternal sunshine.—Alfred E. Smith

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Take particular care in cirrhosis or severe ischemic heart disease and in patients receiving corticosteroids, ACTH, or digitalis. Severe salt restriction is not recommended. Use cautiously in patients with ulcerative colitis or gallstones (biliary colic may be precipitated). Bronchial asthma may occur in susceptible patients.
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Obstetrical Seminar

Prolonged Gestation

THE PROBLEM of the postmature infant represents a disturbance in the time relations of gestation. Prolonged pregnancy was discussed in the medical literature of the 19th century, but it was not until 1902 that Ballantyne[1] brought the problem into focus. Since then there has been an increasing interest in the effects of prolonged gestation on the infant. The center of this interest has been primarily in Britain and on the European continent, but in the past 10 to 15 years increasing note of this topic has been taken in the American literature.

The physiology and symptomatology of many diseases and syndromes are controversial because there is no agreement as to their cause and even as to their existence. Postmaturity belongs to this category of conditions. Some reputable experts deny that prolonged gestation may be harmful to an infant. Those who accept the existence of such a syndrome do not agree as to its specific definition, physiology, symptomatology, or method of treatment. Some laboratory studies have been carried out to support a theory of causation, but the results of these have been promptly refuted.

The purposes of this paper are to present a review of current literature concerning the various clinical aspects of prolonged gestation, to discuss some of the laboratory investigations associated with placental function, and hopefully to draw some useful and practical conclusions from the controversy.

Definitions

The average duration of human pregnancy is usually considered as 267 days when figured from the date of conception or 280 days when calculated from the first day of the last menstrual period. However, the actual duration of pregnancy has a bell-shaped distribution, with the peak incidence of delivery occurring at 40 weeks. Statistical surveys[2] show that 12% of pregnancies go beyond the 294th day and 4% beyond 300 days. Because of this range of delivery dates, the definition of postmaturity has not been agreed on. In his original paper, Ballantyne[1] regarded as postmature any infant who was born after a pregnancy that lasted 10 calendar months (300 days). This definition is accepted by many authors,[2-6] although others[7-10] use 42 weeks or 294 days as the basis for their definition of postmaturity.

Clinical Features

In addition to defining postmaturity in terms of the duration of the pregnancy, Ballantyne[1] described the following associated findings:

1. The weight and size of the infant were almost always above average.
2. The length and head diameter were greater than normal.
3. Lanugo hair and vernix were absent.
4. Redness and desquamation of the skin was pronounced.
5. The fingernails projected beyond the tips of the digits.
6. A plentiful accumulation of subcutaneous fat deposits was present.
7. The child usually had abundant scalp hair.
8. The anterior fontanelle was usually small.
9. Ossification was advanced beyond normal in most bones of the body.
10. The lower portion of the colon was distended with meconium.
11. The bladder was usually full because the placenta was no longer functioning as an excretory organ.
12. The placenta was larger than normal, with microscopic evidence of degeneration and often calcification.
13. The umbilical cord often showed one artery almost closed.
14. The amount of amnionic fluid was less than normal and was often stained with meconium.
15. Toxemia was more common in women with prolonged pregnancy.
16. Labor was usually tedious and long.

The recent literature has included comments on most of the points that Ballantyne has discussed. Magram and Cavanagh[6] and Mead and Marcus[8] agreed with Ballantyne's observation that the size of postmature infants is greater than average; however, many other authors[2,7,11,12] have stated that in prolonged pregnancies babies are rarely of excessive size. Browne[7] and Clifford[11] have commented on the unusual appearance of the skin of these infants; they noted the frequent absence of vernix and the cracked, stained appearance so frequently seen in the skin.

Whereas the excessive placental size as observed by Ballantyne has not received comment by other authors, placental dysfunction has been mentioned most often as the primary cause of postmaturity. Mead and Marcus[8] expressed a typical opinion that placental dysfunction and hypoxia may be definite risks to the infant in a prolonged pregnancy. Clifford[11] incorporated this opinion into the following criteria for staging postmaturity: Stage I is manifested by loss of vernix, dry parched skin, and open-eyed, alert infants. In Stage II, besides the findings in Stage I, the placental function has degenerated, producing fetal distress manifested by liberation of large quantities of meconium in the amnionic fluid, and the skin and membranes are stained with meconium. In Stage III, intra-uterine anoxia is evident by the passing of meconium days or weeks before birth. It was his impression that with progression from the first stage, the outlook for the infant became worse.

Browne[7] probably has been the main spokesman for the British opinion on postmaturity. He stated that in most British hospitals postmaturity is second only to toxemia as a cause for surgical induction of labor. He found that the perinatal mortality rate was lowest at 40 to 41 weeks, that by 43 weeks it had doubled, and by 44 it had trebled. Gibberd[13] in his study of 7,965 births from 37 to 44 weeks reported a perinatal mortality rate of 1.1% in infants of more than 41 weeks' gestation. However, a weekly analysis indicated that the perinatal mortality rate at 41 weeks was 0.4%, at 42 weeks 1.3% at 43 weeks 2.8%, and at 44 weeks 4.3%. Other authors[5,8,9,14-16] supported the supposition that the perinatal mortality rate increases with prolonged gestation. Browne[7] and Mead and Marcus[8] all believed that toxemia superimposed on prolonged pregnancy carries a much greater risk to the infant.

Age and parity apparently also contribute significantly. Browne[7] stated that the risk to the infant is greater in elderly mothers and that primiparous women have more trouble with prolonged pregnancy than multiparous patients. Other writers[4,6,8,11,14,16] also concur on these two points. Browne[7] and others[8,9,16] have found that patients with prolonged pregnancy tend to have longer, more difficult labors than normal and that the first evidence of fetal distress is often seen during labor. Clifford[11] and Smith and co-workers[9] all observed that the amount of amnionic fluid in patients with prolonged pregnancy seems to be decreased significantly. Clifford[11] is the only author who commented about subsequent pregnancies in women who have had a previous infant with the postmaturity syndrome. He stated that 73% of the primigravidas whose period of gestation lasted 300 days or longer did not become pregnant during the following 10 years.

Two authors[1,5] have noted that anencephalic infants are sometimes associated with prolonged pregnancy; however, this probably is a coincidental occurrence and not a cause and effect relationship. Eastman and Hellman[2] stated that only rarely is an anencephalic pregnancy associated with increased duration of pregnancy. Evans and associates[14] stated that the incidence of fetal malposition in prolonged gestation is no greater than normal. Mead and Marcus[8] supported this observation but added that the incidence of midforceps deliveries is increased in prolonged pregnancy. Such operative interference is usually due to fetal distress or lack of progress after a long and tedious labor in which the cervix has finally become fully dilated. They also stated that there is no higher incidence of bleeding or toxemia in women whose pregnancies go beyond 42 weeks. Evans and associates[14] also emphasized that the maternal mortality is not affected by prolonged gestation.

Laboratory Data

Oxygen Supply

In an attempt to substantiate hypoxia due to poor placental function as a major etiologic factor in the postmaturity syndrome, Walker[15] in 1954 studied the oxygen supply to the fetus. His results showed that the oxygen supply to the normal infant decreases gradually up to the 40th week and rapidly thereafter. Most fetuses at 40 weeks are well oxygenated and have 100% reserve, but by 43 weeks all fetuses have low oxygenation and no reserve. When meconium is passed, the oxygen saturation in the umbilical vein is only 30%—a level that is insufficient for the fetus. But other authors[12,17] do not believe that there is enough reliable evidence to substantiate these studies.

Hormone Levels

Laboratory investigations can test the adequacy of placental function by measuring the hormone levels of the placenta. Lundwall and Stakemann[18] and Smith and co-workers[9] studied urinary estriol in prolonged pregnancy. These studies were done on 24-hour urine samples to determine the adequacy of the feto-placental complex, and the authors generally agreed that a decreasing level of estriol occurring after term was an indication of failing placental function. Levels of less than 16 mg in 24 hours were believed to be an indication for interruption of the pregnancy. If the levels were very low—about 8 mg in 24 hours—a cesarean section was done. Otherwise, induction of labor was safe. They emphasized that in borderline cases more than one determination was essential. Two or three tests showing progressively lower levels of estriol were considered very significant; levels of less than 4 mg in 24 hours were associated with fetal death in utero.

Babuna and Yenen[3] did serial tests on serum oxytocinase, which is also produced by the placenta, and found that this test was less expensive and more practical than the serial urinary estriol test because it was done on serum. They noted that in normal pregnancy the oxytocinase levels were low in early pregnancy, increased after the 16th week, reached a peak at term, but decreased in toxemia and in prolonged pregnancy.

Management

Induction at Forty-Two Weeks

Because divergent opinions exist regarding the various aspects of postmaturity, there is no uniform method of management. Browne's method[7] is typical of those in Britain who believe that prolonged pregnancy represents a risk to the fetus in utero. He induces labor surgically at 42 weeks' gestation, whatever the status of the cervix. If abundant fluid is evident when the membranes are ruptured, there is no need to worry about placental reserve. However, if the fluid is scanty, thick, and stained with meconium, he proceeds immediately with a cesarean section because he believes the child will probably not survive the stress of labor. If labor ensues after the membranes are ruptured, he does not allow the second stage to last longer than one hour. Browne[7] believes that pudendal block is the best method of anesthesia and that labor should be induced in toxemic patients after 41 weeks' gestation instead of 42. Walker[15] concluded that primiparous patients who are less than 25 years old should be allowed to go into labor spontaneously. If fetal distress develops during labor and especially if meconium appears in the fluid, oxygen should be given to the mother.

Cesarean Section

In older primiparous women or in those patients in whom a long labor is anticipated, cesarean section should be done at the first sign of fetal distress. Walker further believes that in primiparous and multiparous patients older than 25 years, labor should be induced at the end of 41 weeks' gestation, and that cesarean section is indicated at the first signs of fetal distress. If a patient had had a previous stillbirth, labor should be induced before term. Smith and associates[9] go even farther by stating that when postmaturity has been diagnosed, labor is contraindicated unless the estriol level is at least in the borderline range of seven to 12 mg in 24 hours. They believe that labor eliminates all placental reserve and that cesarean section is the only safe method of delivery for the infant.

Conservative Approach

Other authors take a more conservative approach. Eastman and Hellman[2] considered that since the hazard of postmaturity is less than the hazard of induction, most patients should be allowed to go into labor spontaneously, regardless of the length of gestation. Mead and Marcus[8] agreed with this conservative approach and commented that the proper handling of any obstetric difficulties is more important than setting a deadline for induction. Gibberd[13] in his excellent statistical study stated that if there were a perfectly effective method of induction and it was used in every pregnancy just before 41 weeks, six more babies in every 1,000 inductions would be saved. However, because no infallible method of induction is available, an attempt that fails will needlessly stress an already stressed placenta.

Conclusion and Comment

From this information, some practical conclusions can be drawn. Some infants in the 4% of pregnancies that last longer than 300 days have an increased risk of mortality—either antepartum, intrapartum, or postpartum. The two factors that seem to have a direct bearing on the outcome in the affected infants are the age and parity of the mother. Women more than 25 years old and primiparous patients seem to have babies that are more severely affected by prolonged pregnancy. The infants of multiparous patients, even though the pregnancy is prolonged, seem to suffer no adverse effects.

In gestations that last longer than 300 days, oligohydramnios or meconium-stained amnionic fluid should prompt the physician to terminate the pregnancy in the most expeditious way.

In prolonged pregnancies, when the physician expects that the infant may become compromised, serial tests of urinary estriol help determine the condition of the fetoplacental complex. There does not seem to be enough evidence yet as to the value of the serum oxytocinase test.

Because there can be adverse effects on the infant when toxemia is superimposed on prolongation of pregnancy, patients with significant toxemia should not be allowed to carry their pregnancies past the expected date of confinement.

Accurate determination of the expected date of confinement in every patient is essential and may help prevent some of the worry over prolonged gestation. In most cases of prolonged pregnancy, the difficulty is an error in the calculation of the date rather than an overdue birth. Although Naegele's rule is the accepted method of calculating this date, other means provide useful aids to confirm it. A menstrual history with special emphasis on the length of the patient's normal cycle helps isolate the actual time of ovulation in relation to the duration of the cycle.

Comparison of the size of the uterus at various times during pregnancy with the calculated duration of gestation is useful. The date of quickening should be noted. If there is any serious doubt about the length of gestation, roentgenography at 36 weeks' gestation to determine distal femoral epiphysis may be helpful. When prolonged gestation is a concern, the question often arises about the exact expected date of confinement. Routine notation of all of these factors in every patient can provide a fairly accurate estimate of the length of gestation.

Primiparous patients and those more than 25 years old should be observed very closely when their gestation goes beyond 42 weeks. Loss of weight and decrease in abdominal girth may indicate oligohydramnios. These are the patients in whom urinary estriol studies are probably indicated. Induction of labor with amniotomy and oxytocin (if necessary) is indicated if the patient goes to 43 weeks' gestation, the estriol levels are adequate, the baby seems to be of adequate size, and the cervix is "ripe." If the quantity of fluid is very small and stained with meconium, cesarean section appears to be indicated. In the patient at 43 weeks whose estriol level is borderline or low, or whose cervix is "unripe," cesarean section is the safest method of delivery.

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References may be secured from the author.

To lengthen thy life, lessen thy meals.—Benjamin Franklin

Grand Rounds

The Multiple System Effects of Diphenylhydantoin (Dilantin)

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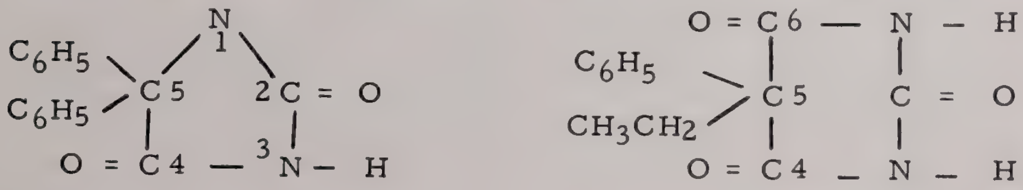
The anti-convulsant drug known as diphenylhydantoin (Dilantin) has been widely used since its introduction in 1938[1] for the control of seizures. It was first considered for the treatment of cardiac disorders in 1950[2]; and the use of the drug in arrhythmias became more widespread after the introduction of a parenteral preparation.[3] Like digitalis, which in some ways has effects quite the opposite of Dilantin, the cellular mechanism of the action of Dilantin is unknown. The drug has widespread systemic effects probably related to a common mechanism, which accounts for its therapeutic as well as its toxic effects.

Chemistry

Structure

Diphenylhydantoin, which is related to the barbiturate derivatives, is basically a substantial five-member ring with two phenyl groups substituted at position five. In the Figure Dilantin is compared to phenobarbital.



Diphenylhydantoin **Phenobarbital**

Figure—Structures of Diphenylhydantoin and Phenobarbital.

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*Presented as a Medical Grand Rounds at Hennepin County General Hospital, April 16, 1968.

Solubility

It is a highly insoluble compound. In direct measurement Dill et al.[4] found a concentration of 14 micrograms/ml. at pH values from 1 to 7. This corresponds to a molar concentration of 0.55×10^{-4} M. At pH 9.1 the saturated solution (in borate buffer) was 0.6×10^{-3} M. At pH 10 it is about ten-fold more concentrated. The pKa was estimated at 9.2. The molecular weight of DPH is about 252. The sodium salt is converted to acid form in the stomach.

Absorption

In the rat, Diel et al.[4] found that oral administration of Dilantin resulted in peak plasma levels in six to eight hours. There was no delay in entering the central nervous system, although the heart concentrations lagged somewhat. At reported doses of 100 mg./kilo, brain and heart levels were 20 and 19 μg/gm. respectively, while liver and fatty tissue levels were higher. Firemark et al.[5] found that brain, plasma and cerebrospinal fluid levels were equal two minutes after parenteral administration. They also reported that brain concentrations exceeded plasma by 10-fold at 24 hours.[6]

In humans given oral Dilantin, peak plasma levels occurred after 12 hours,[4] and the half life of plasma levels was about 20 hours. In dogs the peak plasma level was four hours.

Distribution

Very small quantities of Dilantin are excreted unchanged in the urine: in the dog and human Dilantin is excreted as a hydroxylated derivative. About 50% of an oral dose was found in the urine as the hydroxylated form. An interesting recent report shows that the antituberculosis drug combination, isoniazid and para-aminosalycylic acid reduce parahydroxylation and lead to toxic levels of Dilantin when the latter drug is also being given.[8] Isoniazid and cycloserine also produce the effect, while isoniazid alone has no effect. Folic acid reverses this inhibition, apparently by acting as a cofactor in this detoxification reaction. Other excretion products are hydantoic acid and α-aminodiphenyl acetic acid.[9]

Dilantin is not easily measured, particularly in the presence of phenobarbital, but a recent method is said to circumvent this difficulty. Therapeutic levels in four humans on chronic doses of 100-300 mg. per day orally were in the range of 1-10 micrograms/ml. of plasma.[4]

Toxicity of Diphenylhydantoin

The side effects of this compound are numerous.[11] They include the well known gingival hypertrophy, nystagmus, diplopia, cerebellar signs such as ataxia, skin disorders, megaloblastic anemias, lymphatic hyperplasia, erythoid aplasia, thrombocytopenia and more recently hepatitis. In the acute administration of Dilantin for cardiac arrhythmias, sudden deaths have occurred. This may be related to elimination of a ventricular pacemaker in the presence of high-grade atrioventricular block. A number of these toxic effects will be discussed in more detail.

Megaloblastic Anemia

Megaloblastic anemia associated with Dilantin therapy was first reported in 1950.[12] The cause of this anemia would appear to be folic acid deficiency. In one clinical study folate levels below 2.1 mμ gm./ml. were seen in 35% of a group of epileptics,[13] 11% of whom had macrocytosis without anemia.

In another investigation gastrointestinal function studies were done[14,15], revealing B_{12} and xylose absorption defects in two cases, both of which responded to folic acid treatment. In a third case no clear-cut absorption defect for folate, B_{12} or xylose was found, although a glucose tolerance test before folate treatment was suggestive of malabsorption. A jejunal biopsy was not diagnostic.

Folate levels of less than 5.0 mμg. were found in 58% of 53 patients reported by Klipstein.[15] Slight macrocytosis was seen in 71% of the Dilantin-treated subjects; however, vitamin B_{12} levels were normal. The possible sites of block were reviewed. Folic acid absorption has been said to be normal in the presence of large doses of folate. While some have found increased urinary clearance of folate, this is not a uniform finding. The conversion of dihydro to tetrahydro folic acid does not appear to be affected. Herbert[17] suggested that there may be a competitive inhibition in the conversion of 5-10 methenyl tetrahydrofolic acid to 5 methyltetrahydrofolic acid. Interesting further evidence related to this hypothesis is a recent report of a reversible erythroid aplasia produced by Dilantin in a 17-year-old boy.[17] An immune mechanism was not found to be responsible. Further studies with C-14 formate showed a decreased incorporation of this compound into bone marrow deoxyribonucleic acid. Since labeled deoxynucleotides could be incorporated, in particular deoxyuridilic acid which requires methylation by tetrahydrofolic acid, one must conclude that Dilantin was not inhibiting the folic acid cofactor. The most likely site of block was at the synthesis of deoxyribonucleotides, since none of the precursors of nucleotide synthesis could be incorporated. Ribonucleic acid synthesis was not affected.

A very recent study[19] showed subnormal folic acid levels (<5.0 mμg/ml.) in 54% of 59 children on Dilantin. In a careful oral folate tolerance study in one adult with megaloplastic anemia, inhibition of the absorption of physiological doses of folate (600 μg) were observed to be related to the dose of Dilantin. In this patient, renal excretion and plasma clearance were normal. Conjugase* activity in duodenal aspirates was also normal in this case as well as in four others; however, administration of desiccated chick pancreas caused a hematological response. It was suggested that the chick extract may produce more of the diglutamate form of folic acid which can be absorbed more efficiently.

Cerebellar Degeneration

Slurred speech, nystagmus and ataxia are said to be side effects of Dilantin. The site of the pathology in these cases may be the cerebellum. Hoffmann[20] reported a case of a 28-year-old female who died after a rapidly progressive seizure disorder treated vigorously with Dilantin. At autopsy most purkinje cells had disappeared. Other changes present in the basal ganglia included perivascular cuffing. The author suggests that Dilantin was responsible. In another woman symptoms of nystagmus, ataxia and stupor were noted after large doses of Dilantin.[21] These investigators also found that rats given 200 mg./kilo of Dilantin showed loss of purkinje cells and edema of Bergmann's glia after 14 days. Cats were more sensitive, requiring about 10 mg./kilo for two weeks.

Electron microscopic studies[22] of rat purkinje cells on long-term high doses of Dilantin showed development of membrane concentric bodies (whorls of membrane-like material), shrinkage of purkinje cell bodies, dilation of endoplasmic reticulum and golgi, and increased lysosomes. The glial cells around the purkinje cells, known as Bergmann's glia, also showed morphological changes. Swollen mitochondria were commonly seen. The whorls of membranes were thought to arise from cell membrane structures. An analogy to the lipidoses such as Tay-Sack's disease was suggested because of the similar pathological membrane inclusions.

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*Folic acid in the diet is released from polyglutamates by a conjugase present in duodenal secretions.

Hepatitis

A case of hepatitis following five weeks of Dilantin therapy was recently reported.[23] A biopsy showed hepatocellular injury. After a period of abstinance and then rechallenging the patient with Dilantin, symptoms of drug hypersensitivity reoccurred, although in this brief exposure there was no reoccurrence of hepatic chemical abnormalities.

Lymphadenopathy and Hepatosplenomegally

Although lymphadenopathy is rare,[11] its presence can be confusing in differential diagnosis. A recent report[23] described a case with follicular hyperplasia of lymph nodes and mildly depressed platelet counts after Dilantin therapy. The findings can actually mimic lymphoma or Hodgkin's disease. Seven new cases and a review of the literature were published by Saltzstein and Ackerman.[24] Non-specific hyperplasia of reticulum cells and eosinophilic infiltrations are common, as well as hepatosplenomegally. In another case hepatosplenomegally with lymphadenopathy was reported in a six-year-old child associated with Dilantin treatment. Exfoliative dermatitis and eosinophilia were also present.[26] The lymph nodes are said to be discrete and not matted; Reed Sternberg cells are absent; there is not the uniform appearance of mature lymphocytes seen in lymphosarcoma or chronic lymphatic leukemia.

Fatalities with Dilantin ingestion are rare.[27] The fatal doses in the cases reviewed were 100-200 mg./kilo.

Experimental Basis for the Use of Dilantin in Arrhythmias

The use of Dilantin in arrhythmias was established by experiments of Harris and Kukernot in 1950.[28] There have been many animal and human studies demonstrating its effectiveness. These investigations were summarized by Mercer and Osborne[29] who added a clinical study of 774 patients. They found the best response in ventricular arrhythmias associated with surgery, cardioversion, cardiac catheterization and anesthesia. In 61-82% of the patients the arrhythmia was completely controlled. But in arteriosclerotic heart disease with ventricular arrhythmias complete control was accomplished in only 53%. Supraventricular tachycardias were less well controlled, only 10% of 98 patients being completely controlled. One surprising conclusion was a high rate of success in preventing paroxysmal arrhythmias by chronic oral administration.

Dilantin has been proposed as an effective drug for treatment of digitalis intoxication by Helfant et al.[30]

The toxicity of acetylstrophanthidin was manifested primarily by prolonged atrioventricular conduction, shortened ventricular escape time and ventricular tachycardia. Dilantin converted the ventricular tachycardia and prolonged the ventricular escape time beyond control values; and there was a return of atrioventricular conduction time to near normal value. The effects of Dilantin were in contrast to procainamide, which prolonged intraventricular conduction and further prolonged atrioventricular conduction in digitalis-toxic dogs. In a companion paper[31] the same authors found that pretreatment with Dilantin increased the dose of acetylstrophanthidin necessary to produce ventricular tachycardia by an average of 122% in contrast to procainamide which had no effect. They concluded that the inotropic and arrhythmic actions of digitalis are separated by Dilantin treatment. In humans Heffant et al.[32] demonstrated that Dilantin (5 mg./kilo) significantly decreased atrioventricular conduction time by about 25% at a rate of 100. The decrease was also seen at higher rates. Ouabain-induced prolongations were readily reversed by Dilantin, but no effect of Dilantin on intraventricular conduction time was seen.

Mechanism of Action of Dilantin in Nervous Tissue

The exact effect of Dilantin on nervous tissue is unknown. The drug is used to control grand-mal seizures on a chronic basis and also for status epilepticus. However, a recent study on monkeys by Rand et al.[33] questions the use of intravenous Dilantin in status epilepticus. Directly stimulated cortical potentials were unaffected by the drug at 10 mg./kilo; epileptic foci, chemically induced, were likewise unaffected. Single cell activity in both normal and epileptic cortical cells was unchanged. Spontaneous electroencephalograms of epileptic monkeys were also unaffected. Since Dilantin has been shown to readily penetrate the brain[5] and since other studies have shown that it modifies chemical epileptic foci only when combined with hypothermia,[34] it is concluded that some chemical reorganization of Dilantin at brain-binding sites must occur. There is considerable physiological evidence that it acts at synaptic sites. In the spinal trigeminal nucleus the latency of discharge of single neurons (stimulated from a peripheral site) was increased by intravenous Dilantin.[39] At least one investigator has shown that nerve conduction per se was unaffected in chronic administration of Dilantin[36]; others have reported decreased nerve conduction or synaptic delay, increased threshold, and diminished spike amplitude.[37] In squid, axon electrical activity was altered by Dilantin only when Ca^{++} or Mg^{++} concentrations were altered in the media.[38] A study by Esplin[39] showed that Dilantin inhibits post-tetanic potentiation in cat spinal cord or stellate ganglia. Post-tetanic potentiation is essentially a measure of interneuronal connections. A period of tetanic stimulation of dorsal root fibers or afferent fibers to the stellate ganglia so conditions the pathways that a test stimulus results in an output spike of the ventral root or ganglia of larger amplitude than noted prior to tetanus. Post-tetanic potentiation may result from the partial depolarization of a larger pool of motor neurons, making them more susceptible to firing by a standard stimulus. Dilantin might inhibit post-tetanic potentiation by acting as a hyperpolarizing agent. Synaptic recovery was also found to be delayed by Dilantin. The latter finding could only be attributed to a presynaptic site, since anidromic conditioning did not show such an effect of the drug.

Direct chemical evidence of the mechanism of action of Dilantin is scarce. Woodbury[40] found in acute experiments that Dilantin reduced intracellular sodium concentration and increased sodium turnover in brain. This is consistent with an accelerating effect on the sodium-pumping mechanism with the ultimate effect of hyperpolarizing the neuronal membrane. This effect is not seen in hearts or brains of chronically treated animals.[41] A recent report[42] indicates that Dilantin has no definite measurable effect in doses of 50 mg./kilo on rat brain Na^+ and K^+-stimulated adenosine triphosphatase. It does, however, seem to potentiate ouabain inhibition of this enzyme. Sodium and potassium-stimulated adenosine triphosphatase probably represents a portion of the enzyme system involved in active transport of these ions, i.e., the sodium "pump."

Early evidence by Greengard and Mclwain[43] showed that Dilantin had no effect on resting brain cortex oxygen consumption; however, the drug inhibited the normal increase in respiration observed when the slices were stimulated. Dilantin also prevented the usual decrease in CO_2 production seen in stimulated tissue. Total lactic acid production was not affected. These results suggest some interference with mitochondrial-cytoplasmic coupling.

In a pilot experiment in our laboratory Dilantin injections (5 mg./kilo) intraperitoneally into guinea pigs for ten days had no recognizable effect on brain synapse or brain mitochondrial cytochrome oxidase, nicotinamide adenine dinucleotide diaphorase, or nicotinamide adenine dinucleotide cytochrome c reductase.[44] In other recent studies Dilantin (injected intraperitoneally) was found to have no effect on D-xylose penetration into guinea pig brain slices, while phenobarbital in contrast increased D-xylose penetration at low xylose concentrations and decreased the penetration at high xylose concentrations.[45]

Conclusion and Summary

The mechanism of Dilantin is still not understood. Evidence suggests that the drug acts at presynaptic sites of the nervous system in such a way as to hyperpolarize the cell membrane, thus making the tissue less excitable. A similar mechanism would appear to be involved at the atrioventricular node and in ordinary ventricular muscle. Evidence seems to suggest that sodium pumping gradients may be increased; however, no effect has been seen on that part of the sodium pump which we measure as Na^+ and K^+-stimulated adenosine triphosphatase. But the latter observation does not preclude an effect on the pump, since it measures only a part of the pumping mechanism. Evidence in the cerebellum suggests that membrane turnover and synthesis may be affected.

The contrast with digitalis is apparent; digitalis reduces sodium gradients and partially depolarizes cell membranes, making cells more irritable. Opposite effects from Dilantin are seen in the atrioventricular node and ventricular muscle. With digitalis some of the atrioventricular nodal effects occur via the vagus nerve. Digitalis (in particular ouabain) is well known to inhibit the sodium pump enzyme, Na^+ and K^+-stimulated adenosine triphosphatase, resulting in leakage of potassium from inside the cell and an accumulation of sodium inside the cell. These changes in ionic gradients probably account for the toxic effects of digitalis. The beneficial action of digitalis is probably not related to its inhibition of membrane adenosine triphosphatase which is considered a toxic action. The therapeutic (or inotropic) effect is somehow related to the contraction mechanism itself, perhaps to calcium ion movements between sarcoplasmic reticulum and myofibrils.[46] There must, however, be a coupling mechanism between cell membrane depolarization and the initiation of contraction, perhaps by means of the sarcoplasmic reticulum tubular system. The possibility of separating the two effects of digitalis by Dilantin is an important discovery.

Case Report

A 47-year-old white female was admitted January 12, 1967, from the emergency room with a temperature of 105° rectal and a complaint of dysphagia and garbled speech. She had been an epileptic following a head injury at age 15. She was treated by her private physician until January 11, 1967, when she came to the Neurology Clinic. Examinations at that time showed her to be lethargic and ataxic with ptosis of the right lid. Her medications included Dilantin 100 mg. three times a day and phenobarbital 100 mg. three times a day. An electroencephalogram showed a left temporal lobe epilepsy.

Physical Findings

Physical examination revealed a very pale, febrile, retarded female with flecks of dried blood about her mouth. Positive findings included a flame hemorrhage on the right temporal disk margin, blood in the posterior nasopharynx, and a grade I/VI systolic murmur with a heart rate of 130. Her bowel sounds were active. Generalized lymphadenopathy was noted. Petechiae were present on her legs and a cuff test was positive.

Laboratory Studies

Laboratory work revealed:

Hgb.	4.1 gm.%
Hcrt.	12.1 %
RBC	1.25 x 10^6
MCV	100
MCH	33
MCHC	33
WBC	1,600
Platelets (estimated)	18,000
Reticulocytes	0.5%

A bone marrow was markedly megaloblastic. The peripheral blood smear was hyperchromic and macrocytic with hypersegmented neutrophils.

The spinal fluid was normal. The total serum protein was 6.7 gm.% with 2.9 gm.% albumin. The SGOT was 49; bilirubin and alkaline phosphatase were normal. The BUN was 20 mg.%. A fibrinogen level was normal, but the prothrombin time was 26.7 seconds with a control of 12.6. Urinalysis revealed a 1+ albuminuria; urine culture was negative. Stool guiacs and stool cultures were negative. Sputum cultures showed pneumococci and staphylococcus coagulase positive. Blood and spinal fluid cultures showed only contaminants. A total lactic dehydrogenase on January 15, 1967, was 2850 mu with the heat stable form being 1218. A serum protein bound iodine was normal.

Treatment

The patient was transfused with a unit of whole blood followed by a unit of packed cells. Antibiotic therapy consisted initially of 12 million units of penicillin and 12 gm. of Keflin per day which was later decreased to 8 million units of penicillin and 8 gm. of Keflin. By the eleventh day the patient was afebrile. Urine output was excellent. Folic acid and B_{12} therapy were begun on the first day of admission. On the eighth day she developed a serious nasopharyngeal hemorrhage requiring an anterior pack, and another unit of packed red blood cells was given.

Progress

A number of interesting developments began on the fourth day, three days after the beginning of folic acid and B_{12} therapy. The serum albumin began to fall and the WBC began to rise. On the seventh day the WBC rose to 17,500 and the reticulocyte count to 4.0%. The albumin was now 1.4 gm.% and the BUN, SGOT, and alkaline phosphatase reached values of 30 mg.%, 99 units and 20 units respectively. The BUN and alkaline phosphatase continued to rise. Bilirubin rose to 2.0 mg.% total on the eleventh day. On the tenth day the cephalin flocculation and thymol turbidity tests were abnormal, but rash developed, necessitating the discontinuance of penicillin and Keflin. By now sputum cultures showed Klebsiella enterobacter. The creatinine clearance was 9 cc. per minute, although her urine output remained high.

On the twelfth day a tube feeding was started. On the thirteenth day the patient expired. Post-mortem examination revealed generalized lymphadenopathy with marked lymphocytic infiltration into the liver, kidney and spleen. There was difficulty in deciding whether the infiltration was a lymphoma or a reaction to Dilantin. The latter was the pathologist's final opinion.

The immediate cause of death was most likely inability to clear her thick mucoid respiratory secretions, a problem which had been present from the beginning.

This patient represents at least tentatively a number of complications of Dilantin treatment. There was megaloblastic anemia at this admission. Ataxia and slurred speech had been previously noted, although phenobarbital could have been partially responsible. Lymphocyte infiltration, almost indistinguishable from lymphoma, was present. Her final course showed hepatic and renal failure without eosinophilia, also loss of plasma colloid. These system failures could be due to an allergic phenomenon which she did have; however, the hepatorenal failure exactly paralleled the response of the WBC and reticulocytes to folic acid and B_{12}. One can only speculate that a Dilantin-induced folic acid deficiency held in arrest a Dilantin-induced hypertrophy of reticuloendothelial elements. When folic acid was present, the latter phenomenon was unmasked. This can be compared to the iatrogenic arrest of leukemia by aminopterin.

References may be secured from the Grand Rounds Editor.

Touraine-Solente-Gole Syndrome

This osteodermapathic syndrome is characterized by "bull-dog scalp" lesions involving the scalp, forehead, face, and extremities, elephantiasis of long bones, periosteal lesions, and occasionally pulmonary osteoarthropathy. It was described by Touraine, Solente, and Gole in 1935. The syndrome is limited to males between 25 and 30 years of age.

These abnormalities occur in the absence of any primary disease and involve a combination of cutaneous and osseous tissues. In one reported case pachydermia with extensive folding involved the skin of the head, forehead, cheeks, hands, and feet. Periosteal thickening caused malformation of the hands, which become huge, and enlargement of the feet. These changes involved metatarsal, metacarpal, and phalangeal bones and somewhat resembled the osseous changes of acromegaly. It has therefore been suggested that this disorder may be a variant of acromegaly. The patients' general health may be unaffected. Histologic study of involved skin areas show enlargement and tortuosity of sebaceous canals and an increase in the number and size of blood vessels and elastic fibers. No specific hormonal or other therapy is known.

Durham, Robert H.—Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York

Physician, Cure Thyself

The Arabs, whose scepticism was not confined to matters of religion, avenged themselves to some extent by disparaging verses about doctors, such as the following on the death of Yuhanna ibn Masawayhi in A.D. 857:

"Verily the physician, with his physic and his drugs,
Cannot avert a summons that hath come.
What ails the physician that he dies of the disease
Which he used to cure in time gone by?
There died alike he who administered the drug, and he who took the drug,
And he who imported and sold the drug, and he who bought it."*

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*Edward G. Browne: Arabian Medicine, 1921.

Pediatrics

The Battered Child Syndrome

Part III—Legal Aspects

PRIOR TO 1963, Minnesota had no law governing the reporting of physically abused children. Due to the concern and interest of the medical profession, an amendment was made to the law concerning reporting of gunshot injuries.[1] The recommendation for the amendment came under the direction of the Committee on Child Health of the Minnesota State Medical Association, Dr. Lane Arey, chairman.

In the 1965 legislative session a separate "battered child law" was passed which closely followed the model law as recommended by the Children's Bureau.[2,3] The emphasis for a more workable law for physicians came from the Minnesota Welfare Department and was introduced by Representative Robert G. Renner of Walker, Minnesota. The Minnesota State Medical Association strongly backed this bill.

Further minor changes of the law were made in 1967, as a result of recommendation of students at the William Mitchell College of Law, under their law improvement study (Table 1).

In Hennepin County, from 1963 to 1968, 123* cases of the Battered Child Syndrome have been reported to the Child Protection Division. Seven of these children died; two cases were brought to trial for a crime. Sixteen children were placed in foster homes by court order (legal custody of child given to the Welfare Department). One was committed to a foster home by the court after the mother voluntarily released parental rights. Five cases were handled by criminal court for prosecution of an adult assaulting a child. All defendants were found guilty (two fathers, one mother, one boy friend, one stepfather). One alleged child assault case was heard in Juvenile Court and dismissed, as the court felt evidence of abuse was without foundation.

The law's primary purpose is protection of the abused child who is unable to protect himself. It includes the physically abused child and the "neglected" child. An area which needs further definition and consideration, as suggested by Judge Lindsay Arthur,[4] is that of the emotionally neglected child. Physical abuse is not inflicted upon these children, yet the emotional abuse can be equally as devastating.

"Emotional neglect might be defined as the deprivation suffered by children when their parents do not provide opportunities for the normal experiences producing feelings of being loved, wanted, secure and worthy which result in the ability to form healthy object relationships."[5] From the legal point of view, it is most difficult, if not impossible, to legislate behavioral patterns. Reporting of physically abused children under current Minnesota Law (Table 1) is confined to health personnel whether licensed or not. The report is required to be made to the police and Welfare Department, first orally, then with a written statement. The authors feel that *all* persons, whether health personnel or not, as long as it is done in good faith, should be able to report a suspected child abuse case. Paulsen[6] has criticized this concept, feeling that "everybody's duty easily becomes nobody's duty." The report should name the child, his age, his parents or the people caring for him and their addresses, as complete a history as possible, using names, including that of the alleged assailant, a physical examination, x-ray findings, and such other data as may be pertinent (electroencephalogram, sub-dural taps, surgical results, etc.). Early reporting is essential for the Welfare Department and police to do an effective job.

As soon as a report has been received, the County Welfare Department has the responsibility to investigate the complaints and provide such protection to the child as is necessary until the investigation is completed.

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*Compiled by Mr. Martin Coyne, Unit Supervisor, Child Protection Division, Hennepin County Welfare Department.

If a report is given in good faith the person reporting is immune from liability. If he is called to court to testify, his testimony is not a basis for libel. Thus a physician should not fear suit as a reason for not reporting a possible case of child abuse.

"Privileged communication" does not apply to child abuse cases. Even if it did, it would have to be invoked by the child, and since he is not a party to the litigation, no issue of privilege should arise. This clause avoids this possible roadblock.[3]

The last clause of the law includes a penalty for not reporting a recognized case, which in Minnesota represents a misdemeanor. The maximum penalty for this is an up to one hundred dollars fine and/or up to ninety days in jail. In Wisconsin it is one hundred dollars and/or six months. In Pennsylvania it is five hundred dollars and/or one year.[7]

The general tenor of the law is recognizance of the importance of the protection of the abused child. This is paramount in importance as evidenced by the 10 percent death rate and 30 to 50 percent recurrence rate of the problem.[8] Annually, more cases are being reported reflecting increased awareness of the reporting laws[9] and recognition of the syndrome. When cases are reported, something *is* done by the Welfare Department, and when necessary, legal proceedings are generally directed toward the benefit of the child. Punishment of the assailant usually accomplishes little. Assistance to and protection of the child are the prime goals of the Health personnel, Welfare Department, and legal officials.

Summary

The Minnesota State law concerning reporting of child abuse is discussed. Its purpose is protection of the abused child. Health personnel must report such cases under penalty of law for not doing so. Reporting constitutes *no* basis for liability. Hennepin County experience reflects that reporting does get action appropriate to the individual case.

TABLE I—MINNESOTA STATE LAW

626.554 Reporting of Maltreatment of Minors

Subdivision 1. *Declaration of purpose.* The purpose of this section is to provide for the protection of minor children who have had physical injury inflicted upon them, by other than accidental means, where the injury appears to have been caused as a result of physical abuse or neglect.

Subdivision 2. *Who makes report and to whom made.* Any physician, surgeon, person authorized to engage in the practice of healing, superintendent or manager of a hospital, nurse and pharmacist, whether such physicians, surgeons, persons engaged in the practice of healing, superintendent or manager of any hospital, nurse and pharmacist be licensed or not, shall immediately report all cases of physical injury to children inflicted by other than accidental means which come to their attention where the injury appears to have been caused, as a result of physical abuse or neglect. Such cases shall be reported to the appropriate police authority as defined in section 626.53 and the county welfare agency. The appropriate police authority, upon receiving such a report, shall immediately notify the county welfare agency. Provided however, that no provision of this section shall be construed to mean that a child is neglected or lacks proper parental care solely because said child's parent, guardian, or custodian in good faith, selects and depends upon spiritual means or prayer for the treatment or cure of disease or remedial care of such child.

Subdivision 3. *Nature and Content of Report.* An oral report shall be made immediately by telephone or otherwise and followed as soon thereafter as possible by a report in writing, to the appropriate police authority and the county welfare agency. Such report shall contain the names and addresses of the child and his parents or other persons responsible for his care, if known, the child's age, the nature and extent of the child's injuries including any evidence of previous injuries, and any other information helpful in establishing the cause of the injuries and the identity of the perpetrator.

Subdivision 4. *Responsibility of county welfare agency* The county welfare agency shall investigate complaints of neglect and abuse of children and offer protective social services in an effort to protect the health and welfare of these children and to prevent further abuses.

Subdivision 5. *Immunity from liability.* Anyone participating in good faith in the making of a report pursuant to this section shall have immunity from any liability, civil or criminal, that might otherwise be incurred or imposed. Any such participant shall have the same immunity with respect to participation in any judicial proceeding resulting from such report.

Subdivision 6. *Evidence not privileged.* Neither the physician-patient privilege nor the husband-wife privilege shall be a ground for excluding evidence regarding a child's injuries or the cause thereof, in any judicial proceeding resulting from a report pursuant to this section.

Subdivision 7. *Penalty for this violation.* Anyone knowingly and willingly violating the provisions of this section is guilty of a misdemeanor.

1965 c 758 s 2; 1967 x 322 s 1

From the Department of Pediatrics, University of Minnesota Medical School.

*Medical Fellow in Pediatrics, University of Minnesota.

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Hugh D. Allen, M.D.*
Robert W. tenBensel, M.D.†
Richard B. Raile, M.D.‡
Minneapolis, Minnesota

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Laos

Responsible humans don't avoid decisions. Our problem is sifting out those decisions which concern priority matters. Perhaps our whole life is a struggle to discover what really is important in terms of history and mankind's struggle to find justice, freedom, and meaning in life.

The Advent Season reminds us that God is constantly coming to us in the form of people all over the world who are not reaching their human potential. Inasmuch as we are able, we have accepted our responsibility to live for these and all humanity. This commitment gives us the freedom, and the obligation, to ask you to consider four decisions among your priorities for the coming 30 days:

1. Find a new LAOS volunteer—maybe your family dentist or physician, or a teacher who could give two months during the summer, or even yourself.
2. Arrange for some group who does not know about LAOS to see our filmstrip during 1969.
3. See if you can get LAOS in the budget of your church.
4. Seriously consider investing $15 or more of your own funds in LAOS.

We hope that you will say yes to at least two of these decisions.

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Beware lest you lose the substance by grasping at the shadow.—Aesop

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I am a member of the rabble in good standing.—Westbrook Pegler

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WANTED: Young physician for association leading to partnership with four well established General Practitioners in fast growing suburb of St. Paul. Excellent clinic facilities in nearly new, partnership owned, well equipped, medical center building. Contact: A. Eugene Muller, M.D., North St. Paul Medical Center, 2579 East 7th Avenue, North St. Paul, Minnesota 55109.

THREE MAN group in North West Wisconsin Resort, State Conservation and Retirement Area needs two more physicians adequately to serve their practice. Facilities offered are three-room physician suites, X-ray and lab under AMT technician, RN-only nursing personnel. New accredited thirty-two bed hospital and forty-six bed nursing home. Deer and duck hunting, fishing within five minutes of town. Internist most needed; generalists welcomed. Will meet any reasonable salary request. Partnership after one year. Write: MINNESOTA MEDICINE—365; 375 Jackson St, St. Paul 55101.

GENERAL SURGEON interested in some general practice to associate with a 2-man partnership in a rich agricultural community in southern Minnesota. Modern hospital and new clinic building. Hunting, 9-hole golf course, swimming pool. Salary open and full partnership as soon as desired. Write: MINNESOTA MEDICINE—405, 375 Jackson, St. Paul 55101.

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G.P. AND INTERNIST for five-man clinic. New building, good hospital, city of 14,000 in heart of lake district. Good schools, junior college. Write: MINNESOTA MEDICINE—420, 375 Jackson St., St. Paul.

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EXPANDING EIGHT-MAN CLINIC IN NORTHWESTERN WISCONSIN has immediate openings in General Practice, Internal Medicine and Urology. New clinic building; three accredited hospitals; large branch of the University of Wisconsin; population 33,000. Liberal first year salary, early partnership. Contact Milton Finn, M.D., 3600 Tower Avenue, Superior, Wisconsin 54880. Tel.: 715-392-8111.

THE WEST MEDICAL CLINIC has an opening for a General Practice Physician. This is a five man group that conducts a practice near downtown St. Paul and also has the Airport Medical Clinic at Wold Chamberlain Field, Twin City International Airport. Both clinics have full laboratory and X-ray services with technologists covering both fields.

The Airport Medical Clinic does industrial, occupational and Aviation medicine. FAA examinations are conducted at both clinics.

The clinic located near downtown St. Paul has a practice limited principally to internal medicine, pediatrics, as well as occupational and industrial medicine. There is only a limited practice of obstetrics and no surgery.

Salary is open and opportunity for partnership is available. Write: West Medical Clinic, 539 W. Seventh Street, St. Paul, Minnesota 55102. Phone: Area Code 612-227-9341.

ASSOCIATE urgently needed in busy general practice. Excellent clinic and hospital facilities. Salary open. Partnership after 1 year. Klefstad Clinic, Greenbush, Minn. Call collect: Lloyd H. Klefstad, M.D., Tele. 218—782-5275 or 4725.

TWO MAN GROUP needs a third general practitioner in a fast-growing West St. Paul area. Begin with salary and assume early partnership. Contact N. W. Howe, M.D., or E. J. McEllistrem, M.D., 1246 Gorman, West St. Paul, Minn. 55118 Telephone: 224-8001.

WANTED: G.P. to join clinic serving population area of 12,000. City has new hospital, new clinic building, two nursing homes, new Jr-Sr high school, new swimming pool, rich farming area in Red River Valley. Fishing and hunting nearby; metropolitan city close by. Salary open and partnership if interested. Write or call Warren Clinic, Warren, Minnesota 742-6231, area code 218.

GENERAL PRACTITIONER wanted to join well-established practitioner. New clinic building—90 miles east of St. Paul—city of 14,000. Early partnership with full hospital facilities. Ideal location. L. W. Picotte, M.D.; Chippewa Falls, Wisconsin.

(Continued on page 378)

in cerebrovascular disorders

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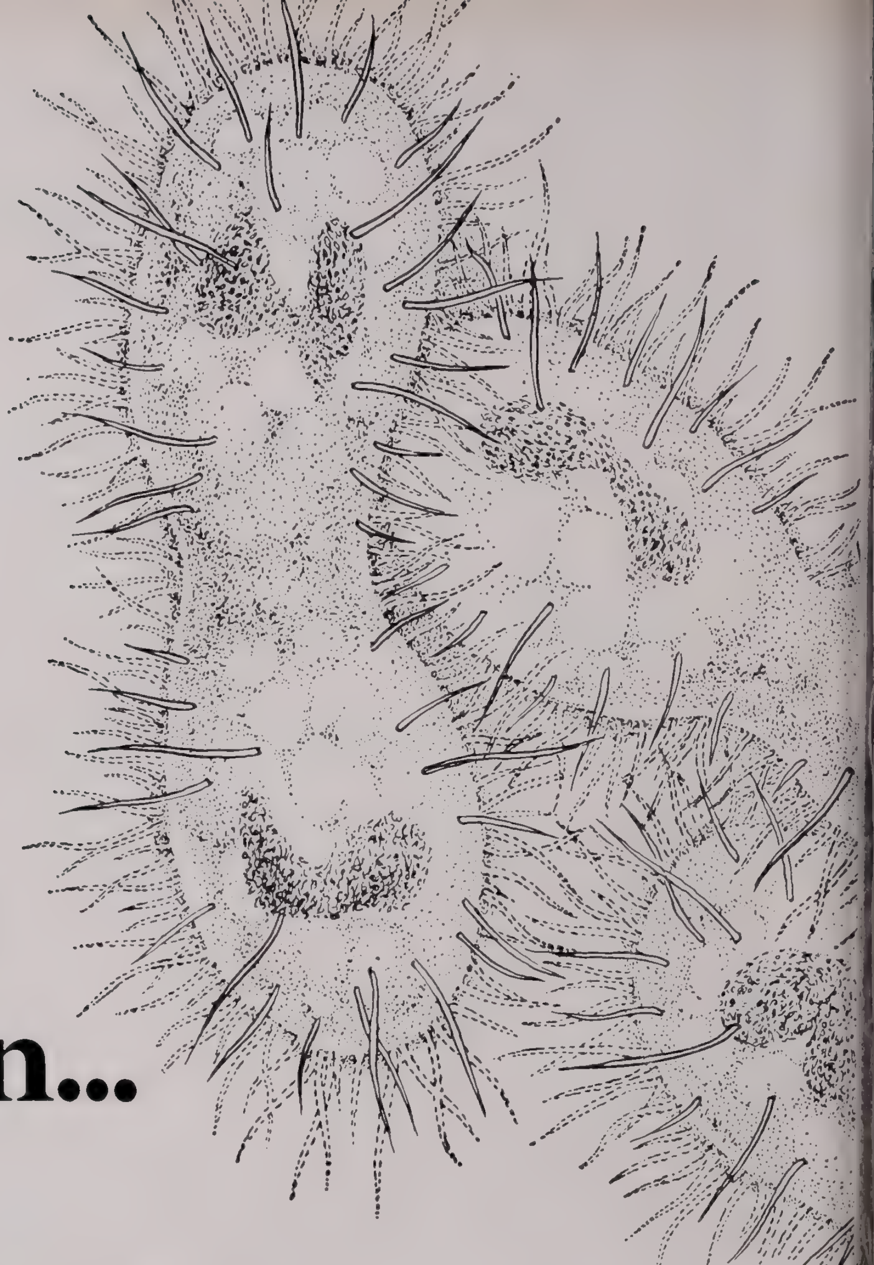

A high index of suspicion... E. coli

How high is the "index of suspicion" for *E. coli* in urinary tract infections?

Recently it has been estimated that about 86 per cent of positive cultures in first attacks of urinary tract infection are *E. coli.*[1] It has also been noted that "The coliform group, especially *E. coli*, accounts for approximately 90 per cent of initial infections...."[2]

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Convenient, economical dosage schedule: *b.i.d.*

References: 1. Vernier, R. L., in Patient Care Feature: *Patient Care, 1*:20 (Feb.) 1967. **2.** Beeson, P. B.: "The Infectious Diseases," in Beeson, P. B., and McDermott, W. (eds.): *Cecil-Loeb Textbook of Medicine*, ed. 12, Philadelphia, W. B. Saunders Company, 1967, p. 230.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Acute and chronic urinary tract, respiratory and soft tissue infections due to susceptible microorganisms; prophylactically following diagnostic instrumental procedures on genitourinary tract.

Contraindicated in sulfonamide-sensitive patients, pregnant females at term, premature infants, or newborn infants during first 3 months of life.

Warnings: Use only after critical appraisal in patients with liver or renal damage, urinary obstruction or blood dyscrasias. Deaths reported from hypersensitivity reactions, Stevens-Johnson syndrome, agranulocytosis, aplastic anemia and other blood dyscrasias. In closely intermittent or prolonged therapy, blood counts and liver and

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Artist's rendition of E. coli. As with most strains of E. coli, these have flagella and are motile.

kidney function tests should be performed. Clinical data insufficient on prolonged or recurrent therapy in chronic renal diseases of children under 6 years.

Precautions: Occasional failures may occur due to resistant microorganisms. Not effective in virus and rickettsial infections. Sulfonamides not recommended for therapy of acute infections caused by group A beta-hemolytic streptococci. At present, penicillin is drug of choice in acute group A beta-hemolytic streptococcal infections; although Gantanol has produced favorable bacteriologic conversion rates in this infection, data insufficient on long-term follow-up studies as to its effect on sequelae of rheumatic fever or acute glomerulonephritis. If other treatment cannot be used and Gantanol is employed in such infections, *important that therapy be continued in usual recommended dosage for at least 10 days.* Observe usual sulfonamide therapy precautions, including adequate fluid intake. Use with caution if history of allergies and/or asthma. Follow closely patients with renal impairment since this may cause excessive drug accumulation. Need for indicated local measures or surgery not obviated in localized infections.

Adverse Reactions: Depending upon the severity of the reaction, may withdraw drug in event of headache, nausea, vomiting, urticaria, diarrhea, hepatitis, pancreatitis, blood dyscrasias, neuropathy, drug fever, Stevens-Johnson syndrome, skin rash, injection of the conjunctiva and sclera, petechiae, purpura, hematuria and crystalluria.

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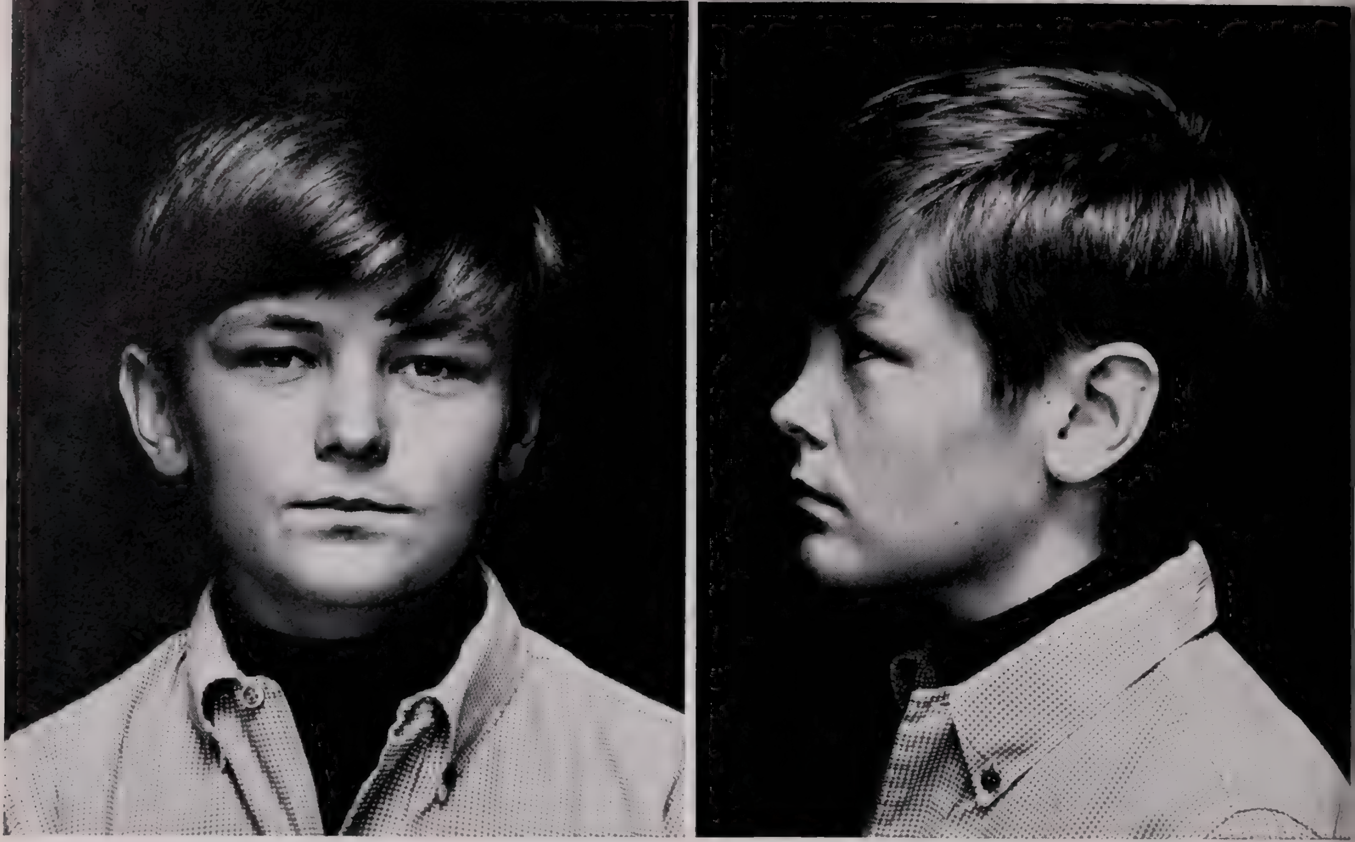

How to turn a 14-year-old boy into a hardened criminal.

Just forget your keys in your car one day.

Tempt some fourteen-year-old boy into going for a joyride.

Oh, he could be a good kid – just weak.

And taking your car might be the first time he's ever broken the law.

But the minute he hops behind that wheel and turns the key, his life may be ruined.

He'll drive around for a few hours, endangering the life of every man, woman and child who crosses his path.

He might be caught the very first time he takes a car. Or if he's not caught by the police he'll leave your car somewhere and decide to do it again, and again, until the day he does get caught.

Teen-agers steal more than 1,000 cars every day.

The U. S. Department of Justice and your state and local law-enforcement agencies are concerned.

They know that taking a car for a joyride is just the first step.

Our prisons are filled with men who started out this way. They went on to become thieves, muggers, and even killers.

You can do something to help solve this terrible problem.

Whenever you get out of your car, even for a second, take your keys. Lock your car.

Every time you do this you may keep a good boy from going bad.

Don't help a good boy go bad. Lock your car. Take your keys.

Abstracts, Briefs and Commentaries

CANCER OF THE COLON: THE INFLUENCE OF NO-TOUCH ISOLATION TECHNIC ON SURVIVAL RATES

It has been long suspected that cancer may be disseminated through the blood stream by the trauma of surgical removal. Tyzzer, investigating breast tumors in mice, suggested that cancers of the breast may be explosive. In 1952 Barnes described a special technic for resection of the right colon. He advocated ligation of the vascular pedicles with division of the vessels before handling the cancer-bearing segment. Cole et al. (1954) reported finding cancer cells in the portal venous blood of a perfused resected cancer-bearing segment of the colon. This gave rise to their suggestion that the vascular pedicle be ligated before bowel resection. In 1955 Fisher and Turnbull reported cancer cells in the portal venous blood of eight of 25 resected segments (for cancer) of the colon.

In 1953 Turnbull, Jr., adopted a technic in which the vessel pedicle is ligated with lymphatics before the tumor is palpated, coining the term no-touch isolation for the procedure. In every cancer of the colon operated on by Turnbull, this technic was employed; five other surgeons employed the conventional method. Cancers of the colon were defined as located more than 5½ inches above the anus and were divided into four groups: Stage A- tumor confined to colon and its coati; Stage B- tumor extension into pericolic fat; Stage C- tumor metastases to regional mesenteric glands; Stage D- tumor metastases to liver, lung, etc.

Data on 896 patients were suitable for analysis, with an operability rate of 96%. Six hundred and sixty-four were treated by the author, using the no-touch technic; five other surgeons operated on 232 patients, employing the conventional technic. The resectable rate was 84.2% in both groups. The five-year survival rate was 46.9% for all 896 patients, which is unusually high (usual rates 25-35%.) Deaths from metastatic cancer were more frequent during the first two years after the conventional technic resection, most of them due to metastases to the liver. It is suggested that fatal hepatic metastases may be due to operative manipulation of the cancer-bearing segment.

The survival rates for both methods are about the same after two years; but the true value of the no-touch technic is obvious when the survival rate of the two methods is compared for longer periods of time. The five-year survival of Stage C- cancers (regional glands involvement) is 57.84% by the no-touch method, but 28.06% by conventional methods.

Note: Many years ago Dr. R. E. Farr, with whom I was associated, strongly advocated the no-touch technic in general surgery whenever possible. It is especially desirable when dealing with carcinoma and perhaps infections. It seems definite, as shown by Cole and others, that malignant cells and bacteria can be expressed through both venous and lymphatic tracts.

Stanley R. Maxeiner, Sr., M.D.
Minneapolis, Minnesota

Turnbull, Rupert B., Jr.; Kyle, Kenneth; Watson, Frank R., and Spratt, John: Cancer of the Colon: The Influence of No-touch Isolation Technic on Survival Rates.

GYNECOMASTIA

By definition gynecomastia implies a circumscribed potentially reversible enlargement of the male breast resulting from a combination of causes and a variety of histologic changes.

Gynecomastia results from a hormone imbalance which may likewise be produced by a variety of conditions. Most of these result in the production of an imbalance of the estrogens or endrogens.

Among the most common underlying diseases are hypertension, diabetes mellitus, cirrhosis of the liver, bronchogenic carcinoma, rheumatoid arthritis, generalized non-specific dermatitis, chronic pyelonephritis, arteriosclerotic heart disease and congestive failure. In most of these instances an abnormal production of estrogen has been stimulated by the disease or the medication that has been prescribed.

Carl O. Rice, M.D.

Gynecomastia, Wheeler, Coley, Gray: Ann Intern Med 30: 985, 1954.

IN-PATIENT CHILD PSYCHIATRY AT THE UNIVERSITY OF MINNESOTA

A full-time psychiatric service to children has been included at the University Medical School and Hospitals since 1938. This was initially out-patient; an in-patient service for children began operating in 1952. We provide training for psychiatry residents who rotate through the service, for psychologists, and for medical students.

Our goal is primarily that of diagnosis and, occasionally, extended treatment of psychiatric disorders in children and younger adolescents. Each patient is given a complete study which includes a detailed medical and psychiatric history, a physical examination, psychological testing and, where indicated, a neurologic consultation. We have found it best to have adequate contact with the parents or parental substitutes before admission so that they are familiar with our program and will cooperate with us.

The following diagnostic categories were most frequent: 34% of the children were listed as adjustment reaction of adolescence, and 24% as adjustment reaction of childhood. Nineteen percent were diagnosed as a primary mental retardation.

We are planning to keep some children for a longer period of time and to provide residential treatment for them. They will be selected on the basis of our patient population and staff interest; we have not yet decided if we will concentrate on long-term treatment of a specific disorder.

Michael F. Koch, M.D.
Minneapolis, Minnesota

TOXIC MEGACOLON IN TRANSMURAL COLITIS REGIONAL COLITIS, CROHN'S DISEASE

Toxic dilatation of the colon or toxic megacolon is recognized as the most dreaded complication of fulminating chronic ulcerative colitis. It is also a dread complication of transmural colitis (Crohn's disease of colon). In general the patients with toxic megacolon in transmural colitis were women less than 35 years of age, the range being from 16 to 64 years. Symptomatology fell into two classes: those with a relatively short history of disease, one to six months, and those with a long history of remitting disease. The clinical features resembled exactly the disorder when observed in the course of chronic ulcerative colitis, including fever, disproportionate tachycardia, cramping abdominal pain, abdominal distention, leukocytosis, hypoalbuminemia and hypokalemia. Medical management in these cases was extensive and included adequate intravenous therapy to maintain fluid, electrolyte and protein levels, together with the appropriate antibiotics, corticotrophin, and steroids. In many cases surgical intervention was necessary. In some cases where the patients' condition permitted, they were treated by subtotal or total colectomy and ileostomy; in the more severely ill patient ileostomy and transverse colostomy proved to be life-saving. Pathologic examination of these specimens revealed evidence of fulminant disease, clearly transmural, but with less fibrosis than is usually seen in transmural colitis. Most of the specimens were of a nongranulomatous variety.

W. A. Hawk, M.D., B. Turnbull, Jr., M.D., G. Farmer, M.D.,*
Cleveland, Ohio

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*Cleveland Clinic, Cleveland, Ohio.
Abstract of presentation made during Congressus Gastroenterologiae Internationalis, VIII, in Prague, 1968.

AMEBIC GRANULOMA OF THE COLON, RECTUM AND ANUS

The 11 cases presented clearly show the necessity of very thorough examinations of the stools for ameba in all cases of anal, rectal or colonic disturbances, especially the chronic ones, in which a mass or ulceration is found. If amebas are discovered together with a filling defect in the colon, an ameboma should be suspected and therapeutic trial with antiamebic drugs is indicated before operation is performed. The great majority of amebomas disappear completely within a month of treatment. It is also worthy of emphasis that both amebic colitis and ameboma may coexist with a carcinoma of the colon. I feel that all this is very important in this jet age when transportation is so fast and easy that hundreds of people travel daily back and forth from areas where amebiasis is endemic and are exposed to the disease. Since amebic granuloma is often and easily mistaken for other inflammatory lesions or neoplasms of the anus, rectum and colon the surgeon must never underrate the importance of the early history; and exhaustive search for amebas must be made in order to avoid disastrous operations which unfortunately still take place.

F. Ruiz-Moreno, M.D.*
Mexico City, Mexico

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*Center of Proctology, Mexico City.
Abstract of presentation made during Congressus Gastroenterologiae Internationalis, VIII, in Prague, 1968.

TESTICULAR TORSION

Angell reports 16 recent cases of torsion of the testicle. Disturbingly few cases are diagnosed in time to save the organ. Many are wrongly treated, masquerading as epididymitis, and proceed unchecked to testicular atrophy. Two mistaken beliefs are responsible: that torsion is uncommon and that it seldom resembles inflammation.

An appreciation of the anatomical anomaly in torsion of the fully descended testicle is essential for correct diagnosis and treatment. The two layers of the tunica vaginalis, which normally invest the testis alone, extend upward to cover the whole epididymis and the cord, sometimes as high as the inguinal canal.

In addition, the testis is often separated from the epididymis by a lengthened mesorchium, longest at the upper pole, which enables the testis to lie horizontally when the patient is standing. Or it may be that, although the epididymis is closely applied to the testis, the structures of the lower part of the cord are loosely adherent to the epididymis and thus allow the horizontal disposition of the whole testicle. In this series the anomaly was always bilateral, and the general view seems to be that this is the rule.

The patients' ages ranged from eight to 30. The majority were teenagers; one was under 10, three were over 20. The right testis was affected in 11 patients, the left in five.

All the patients seen during an attack were febrile. Temperatures ranged from 99° F within a few hours to 103° F later. In one patient abdominal pain and vomiting preceded other symptoms for a whole day, and appendicitis was suspected.

In all the 13 patients examined standing, the unaffected testicle could be seen lying horizontally. This sign could be clearly demonstrated even in cases with much scrotal redness and edema.

In only four of the 16 cases was the correct diagnosis suspected by the doctor who first saw the patient; eight were diagnosed as epididymitis, one as hysteria, one as appendicitis, one as spermatocele; and in one no diagnosis was offered. Moreover, seven were initially diagnosed and treated as epididymitis after admission to a surgical ward, for periods varying from a few hours to 14 days.

Regardless of fever, boys and young men with painful scrotal swellings, however inflamed these may look, should be examined standing up in spite of the additional pain this may cause. If the unaffected testicle is seen to lie in a horizontal plane, no diagnosis but torsion should be entertained.

Courtesy of World-Wide Abstracts

Angell, J.: Lancet 1/7271:19.

School of Salernum

Good dyet is a perfect way of curing:
And worthy much regard and health assuring.
A King that cannot rule him in his dyet,
Will hardly rule his Realme in peace and quiet.
—Regimen Sanitatis Salerni

Editor's note: We agree unequivocally that good nutrition and moderation are the keynote to health and the hallmark of a statesman.

Book Reviews

Through his reading a man comes to the cities of the mind.—Lynn Hough

MODERN TREATMENT, VOLUME 5 #4 Treatment of Fluid and Electrolyte Imbalance Special Article, Current Treatment of Clinical Tetanus Guest Editor: David D. Thompson, M.D., Authors: Herman A. Christensen, M.D. and Deloran L. Thurber, M.D., Publishers: Hoeber Medical Division, Harper & Row, 49 East 33rd Street, New York, New York 10016. Price: $16.00 per yr.

The July issue of Modern Treatment contains 110 pages devoted to Fluid and Electrolyte Therapy and a special section of 25 pages on the Current Treatment of Clinical Tetanus. There are 15 contributing authors whose material is edited by David D. Thompson, M.D., Professor of Medicine, Cornell University, Medical College, New York.

This particular issue of Modern Treatment is a very useful and, I believe, well-designed handbook of quick reference on Fluid, Electrolyte and Acid Base Disturbances. Editorial headings and title arrangement make for convenience as a handbook. The short but meaty sections constitute a quick reference source.

The section on the Treatment of Clinical Tetanus brings one up to date on all modern aspects of treatment in this catastrophic disease. A very satisfactory summary is followed by a list of some seventeen references for more detailed information.

J. H. Strickler, M.D.
Minneapolis, Minnesota

SKIN REACTIONS TO PRIMARY IRRITANTS IN PATIENTS WITH HAND ECZEMA (AN INVESTIGATION WITH MATCHED CONTROLS) —By Alf Bjornberg, Oscar Isacsons, Tryckeri AB, Goteborg, Sweden, 1968, 208 pages.

Primary irritants often cause a dermatitis upon contact with either normal or eczematous skin. They include alkalis, acids, and other related substances causing cytotoxic damage. This is in contrast with contact allergens which cause a dermatitis through an indirect immunological reaction.

Primary irritants play an important role in occupational dermatitis. Recent studies show that at least half of all occupational dermatitis is due to these substances. Weinberger in 1950 demonstrated that 80% of occupational dermatoses in his series were due to primary irritants. The monograph under review here attempts to answer several important questions regarding primary irritant dermatitis.

It is interesting that in Bjornberg's study he defined hand eczema morphologically but did not classify it as to etiology. However, dyshydrotic and atopic dermatites were excluded. The primary irritants to be tested were carefully controlled as to concentration, and care was taken that exactly the same site on all individuals was tested. This precaution was taken because there appear to be variations in regional skin reactivity to various primary irritants.

This study concluded that there was no increase in skin reactivity to primary irritants in those patients whose hand eczema had been healed for at least three months. However, it was demonstrated that even a localized eczema, when active, may increase the skin reactivity to some primary irritants but not to others. An important finding was that the alkali neutralization and alkali resistance were unaltered even in patients with localized hand eczema. This finding is important for those who would use these tests either as a prophetic or diagnostic tool.

Willard C. Peterson, Jr., M.D.
Minneapolis, Minnesota

THE CARE OF THE RHEUMATOID HAND (Second Edition)—By Adrian E. Flatt. 234 pages. 112 illustrations. Published by The C. V. Mosby Company, 1968. Price $14.00.

Dr. Flatt has shown great enthusiasm and more than fair success in his development of metallic prosthetic replacement for metacarpophalangeal and proximal interphalangeal finger joints. From his experience at the University of Iowa comes this fine little book aimed directly at the hand surgeon. His descriptions of surgical solutions to rheumatoid hand problems are delightfully clear and brief, with excellent illustrations. The text is of lesser interest to the internist or general practitioner except to inform him of the early surgical treatment available to his patients. The last thirty-five pages outline a ten-year follow-up of various operative procedures in many patients.

Recommended for the orthopedic or hand surgeon as a textbook to be followed. The discussion of operative indications and technique and of expected end results leaves very few questions unanswered.

Robert M. Barnett, M.D.
Minneapolis, Minnesota

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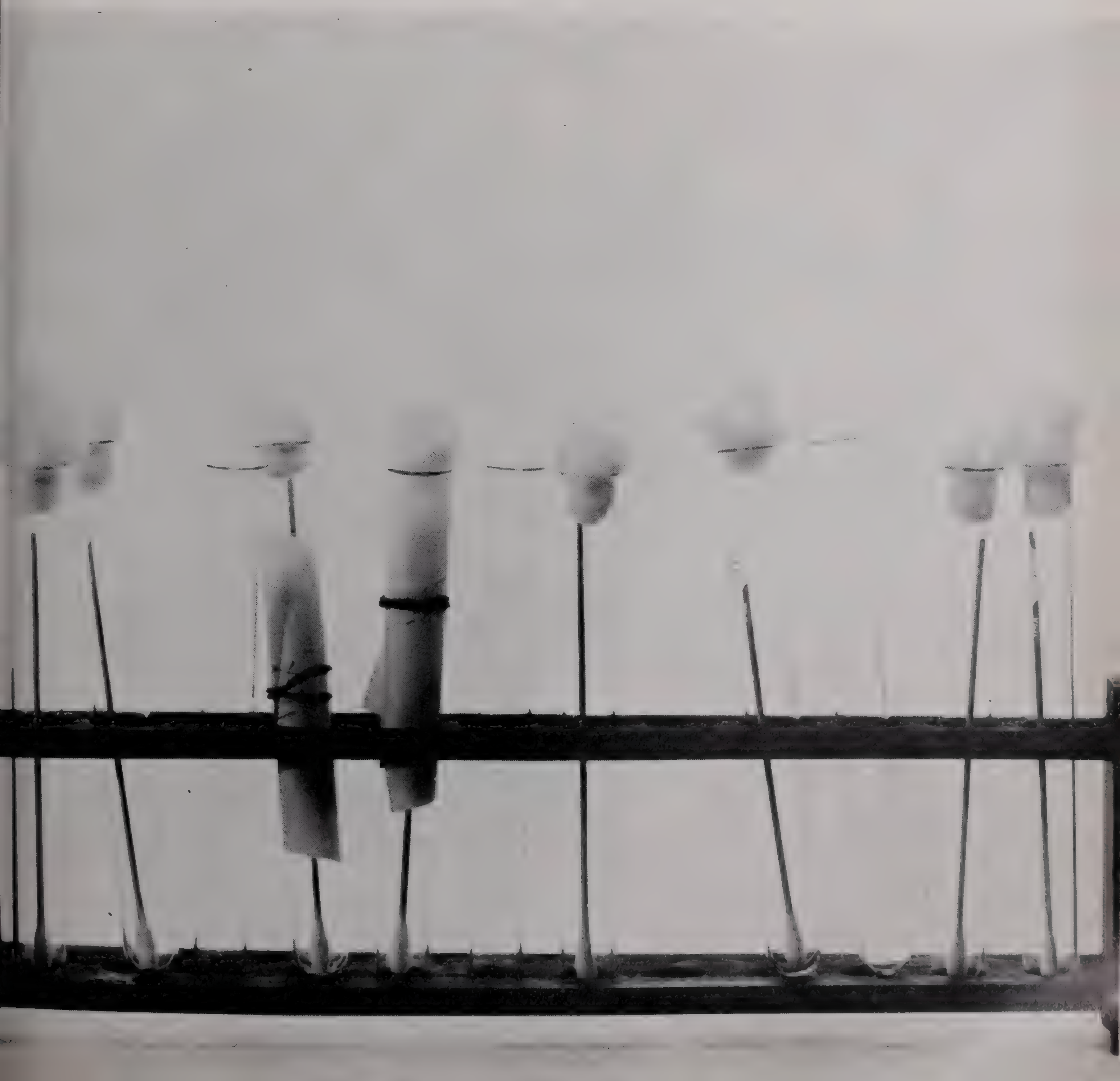

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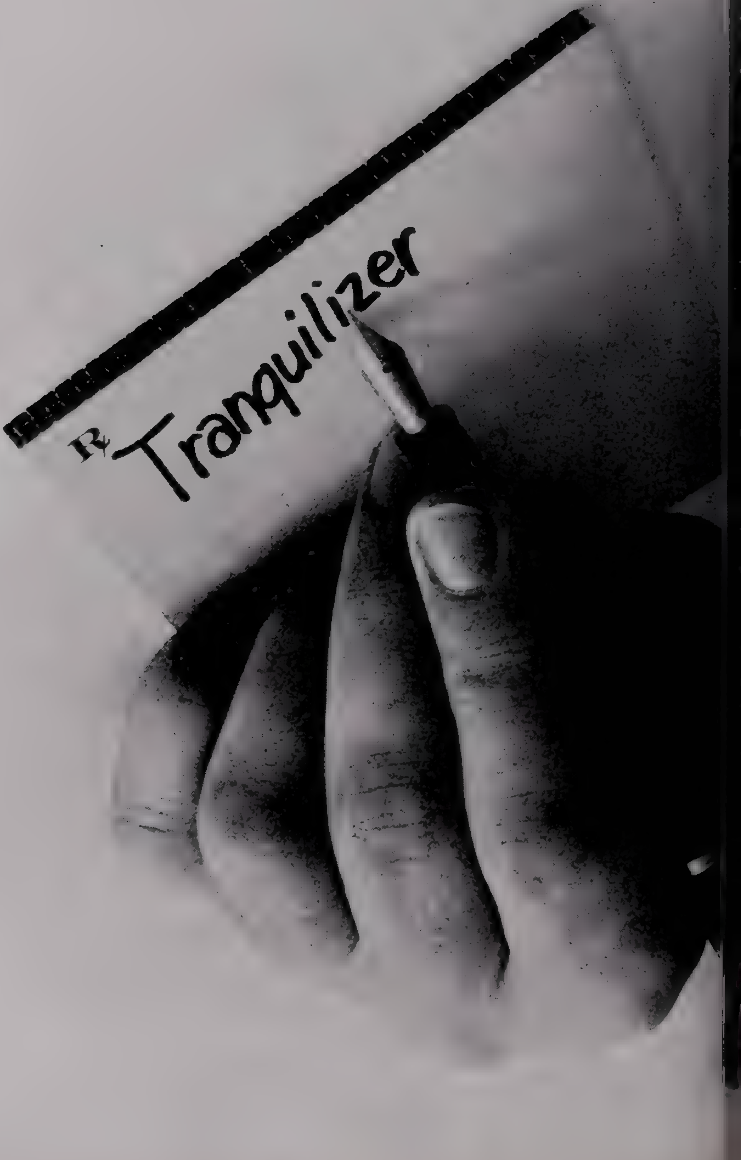

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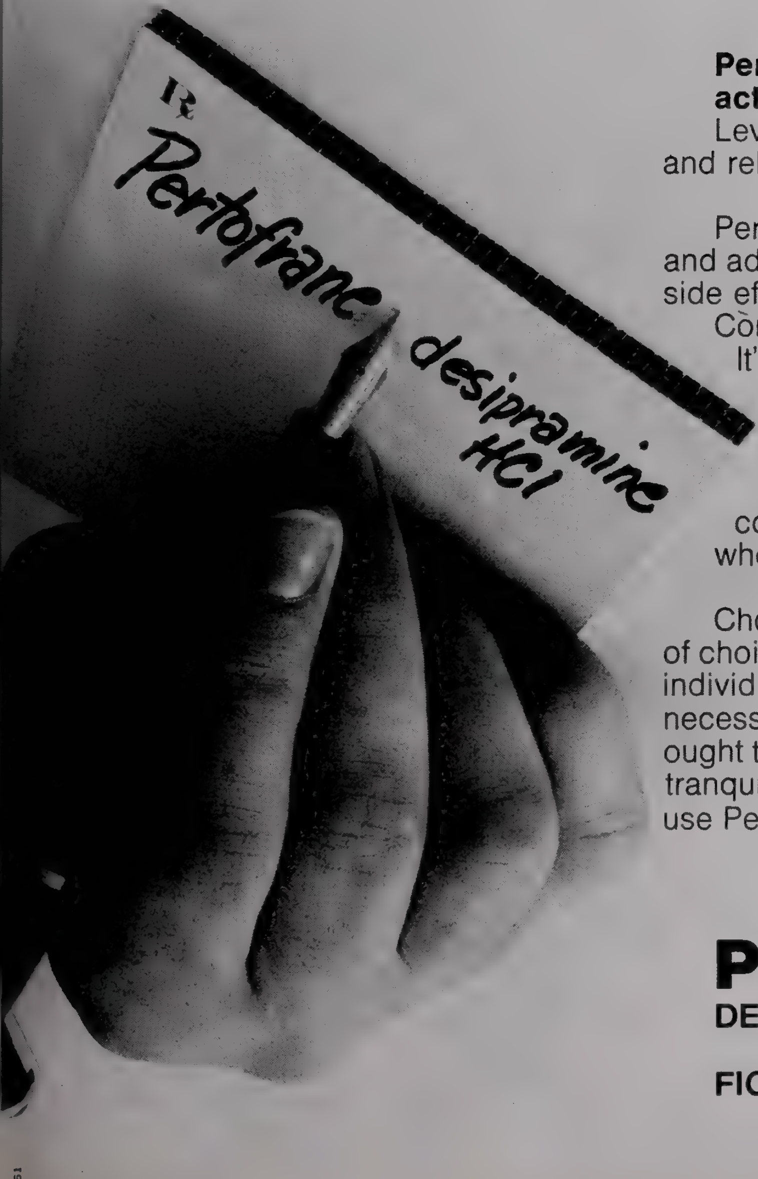

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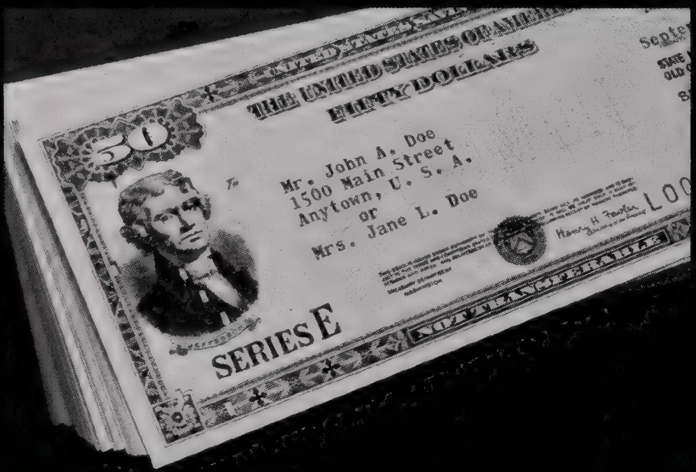

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General Practitioners

General Practice

IS IT DEATH—OR—REJUVENATED LIFE—for the General Practitioner? The Chief of Otolaryngology at an Eastern school predicted Death: "This year of the big look at medical education recognizes that general practitioners will soon be a thing of the past. No longer should medical schools be designed to produce general practitioners . . ."[1] The Millis Report on the other hand foresees Rejuvenated Life: "It is time for decisive action to increase greatly the number of physicians who will devote their professional careers to the highly competent provision of comprehensive and continuing medical services. . . . If organized medicine does not take the leadership in meeting this problem, others will."[2] The ad-hoc committee of the AMA feels that the American public does want and need a large number of well qualified family physicians if the people are to receive the maximal benefits from American Medicine.[3] Such controversy, particularly as it becomes more vocal, is certainly focusing on the fact that two distinct philosophies have emerged today. The one, Complete Specialization; the other Family Practice with consultant referrals. The problem really comes down to the question: Can the best medical care for the people of the United States be given by the family physician with referrals to the appropriate consultant, or can the people get the best care by taking each problem directly to a specialist. Being General-Practitioners and vitally interested in the controversy, we decided to gather statistics and to formulate an explanation from data acquired in our own general practice which present the story to medical educators and students.

Basics of the Study

We are a three-man group, in general practice for about ten years and on the staffs of three hospitals. We have capable professional personnel who handle the nursing and laboratory procedures very efficiently. Our facilities and equipment allow us to practice office medicine in a careful, thorough manner. We chose to tabulate our segment of general practice; every office visit made to our three-man general-practice group over a period of twelve months.

The following table is the compilation of these visits. There are 24 categories and each is listed in the order of its frequency. These categories are based on a combination of regional body systems and pathological state systems. Category 25, "Allergy," lists separate visits for desensitization injections. Category 26, "Immunization," is a part of well baby or school physical visits (diphtheria, pertussus, tetanus, polio, etc.). Category 27, "Antibiotics and Others," tabulates injections of a therapeutic nature for already listed visiting patients.

Problems

The greatest problem in establishing meaningful categories to properly explain the work load of a General Practitioner defies categorization or fragmentation because its essence is the care of the whole person in relation to his family and environment. In reality, a patient visit frequently includes more than one aspect of illness or concern.

Rarely does one treat a specific aspect of illness without including relationship to family and environment. The psychosomatic aspect of medicine is so common that we were perplexed how to indicate it and concluded by eliminating it as a category. During a two-week period one member recorded the patients referred to a consultant, and these represented 4% of his cases seen during those two weeks.

Emergency room and in-patient hospital care, although a major part of Family Practice, were not included in this study, though we do have a hospital practice which totaled 6,833 visits for the year. These 6,833 visits included cases in all major and most minor branches of medicine and surgery.

There is the inevitable human error in recording all the cases seen. The main office listed 17,713 visits, while we three doctors tabulated only 15,674: an error of 12%. The

TABLE I

		Doctor A		Doctor B		Doctor C	
Rank-Categories	Total Visits	Patient Visits	Rank	Patient Visits	Rank	Patient Visits	Rank
1. Ent-URI	2,995	1,448	1	847	1	700	1
2. Ob	1,488	236	5	750	2	502	2
3. Well Baby	1,128	204	7	594	3	330	4
4. Surgery	724	261	3	163	9	300	5
5. L. Resp.	688	311	2	155	10	222	6
6. School PX	677	248	4	277	5	152	11
7. Cardio-Vas.	655	102	12	216	6	337	3
8 Gyn	599	99	13	346	4	154	10
9. Skin	596	202	8	202	7	192	8
10. Ortho	588	230	6	195	8	163	9
11. G.I.	418	156	9	120	12	142	12
12. Metabolic Dis.	348	50	18	88	15	210	7
13. Comp. Physical	330	133	11	102	13	95	14
14. Trauma	282	146	10	39	20	97	13
15. Fracture	229	69	15	95	14	45	16
16. Laceration	206	52	17	145	11	9	21
17. Psychiatric	205	89	14	81	16	35	18
18 G.U.	165	54	16	46	19	65	15
19. Sprain	122	42	20	24	22	56	17
20. Neurology	160	89	21	50	18	21	20
21. Eye	103	45	19	36	21	22	19
22. Procto	62	4	23	50	17	8	22
23. Burns	36	19	22	10	24	7	23
24. Tumors	29	3	24	24	23	2	24
25. Allergies	1,385						
26. Immunizations	1,730						
27. Antibiotic & Other	1,626						
Total Office Visits			17,713	Total Hospital Visits			6,833

first six categories make up almost 50% (49.1%) of all the visits. We were surprised to note that we had performed 330 exhaustively complete examinations which included rather extensive laboratory work.

Unfortunately we did not total the percentage of unusual cases, but a listing of a few of the unusual cases follows:

Pediatrics

Neurogenic diabetes insipidus
Viral encephalitis with bulbar-paralysis
Agammaglobulinemia
Scleroderma neonatorum—3 cases

Surgery

Carcinoid of the rectum (primary)
Fracture of odontoid process—traumatic
Acute ruptured duodenal diverticulum—peritonitis
Acute abdomen — first post-partum day — carcinoma ascending colon with perforation. One year later a second primary carcinoma of the sigmoid colon was found.

Medicine

Addison's disease—two cases
Mondor's Syndrome
Bilateral polycystic kidneys—age 39
Thyroiditis—several cases

Ob-Gyn

Primary carcinoma pericardium—6 mo. pregnant
Third trimester bleeding—transverse—presentation —placenta previa
Serous cystadenocarcinoma of the ovary

Knowing the Family.

Medical care is not just diagnoses and prescriptions. It is knowing the family: the members, their relationship, their finances, their philosophies. It is knowing their environment: their home, their place of work, their schools, their places of leisure. The social aspects of living must be included in medical care lest the results be unsatisfactory. In our particular office we acknowledge the family as the unit of social relationship by having family folders, which allow family data to be immediately available for correlation.

Medical Clerks and Midwives?

If we accept the prediction that the death knell of the General Practitioner has been sounded and that all medicine must be specialized, we then inherit the problem of the patient having to make his own diagnosis prior to choosing the appropriate specialist. One solution has been to educate "medical clerks," but would their diagnosis be an improvement over a Family Physician's? The specialist who says the General Practitioner must not deliver babies proposes to educate midwives to take the place of the General Practitioner. Would this be an improvement in obstetric care? We hear the cry for more pediatricians. Would it be an improvement to eliminate the pediatric care that can be given by the general Practitioner? Who then would take care of the children; who would supervise the school health programs and the preventive-medicine programs?

Most important, the more specific the Specialties become the more fragmented becomes medical care and the more like an "It," a disease problem, becomes the patient. Although there is great emphasis on the need for comprehensive care or patient oriented care, this seems far from actuality at many medical schools. There is a great tendency to encourage earlier and earlier specialization in the medical school curriculum; it has already entered the third year training in some schools. Further along there are great pressures to encourage a non-rotating internship. And now that the student has segregated himself quite thoroughly from relation to the total patient, he completes his training in a residency which confines his thinking to the same field. Is it any wonder that the absurdity of an M.D. completing his internal medicine residency without ever doing a single pelvic has actually occurred? This is quite a contrast to a few years ago when many medical educators were quite definite about the excellence of a year in Family Practice prior to entering a specialty field.

The Hill Foundation and the legislators have shown interest in the need for family physicians and for their training, and out of their findings a recommendation was made to establish the Department of Family Practice at the University of Minnesota to substantially increase the number of family physicians. The U. of M. Medical School officially founded a Department of Family Practice in 1967. It was with keen interest and great hope that the practicing physicians of the state looked toward this new department of medical education. Its doors have not opened as yet—and reasonably so—for the result must be *excellence*.

Training

It is most interesting that Sir William Osler in 1892 spoke on this subject at the University of Minnesota. "The aim of a school should be to have these departments in the charge of men who have, first, *enthusiasm*, that deep love of a subject, that desire to teach and extend it without which all instruction becomes cold and lifeless; secondly, a *full personal knowledge of the branch taught;* not a secondhand information derived from experimental work. . . . Thirdly, men are required who have a *sense of obligation*, that feeling which impels a teacher to be also a contributor."[6]

The faculty and the curriculum and the attitudes must inspire students to enter Family Practice. It must be developed courageously, unmindful of the pressures of special disciplines which would minimize and belittle the effective scope of its care. "It is time for a revolution, not a few patchwork adaptations."[8] Graduate schools still think their primary problem is to ensure professionalism and to train men to do replicate research. The more professionalized men become the more they tend to work on questions which will advance the discipline and the less they care about questions which have genuine significance for the scholar or for laymen outside the university. That the discontent with self-centered professionalism will allow change to creative and socially relevant scholarship is only a hope at this time.[9]

Conclusion

General or Family Practice is a valuable, efficient means of quality medical care. But, can the family practitioner be expected to have the knowledge to care for the wide variety of medical problems which present themselves in his practice. No, he cannot be expected to treat *all* problems as best possible, but, he can be expected to treat *all common* problems as best possible. *Common* is used here to denote frequent occurrence and familiar situations. This includes serious as well as minor illnesses—myocardial infarction, diabetes mellitus, as well as tonsillitis, inguinal hernia, etc. There is the *common* in every field of medicine. The *common* from each field can be delineated, defined and combined to make up the "Core Content" of Family Practice. Because a Family Practitioner can direct his attention to these *common* illnesses, it is thoroughly feasible for him to know and be able to give the best treatment for them. The unusual, the unfamiliar illness, can again be best treated through the General Practitioner for he is eminently better qualified than the patient to choose the best consultant when referral is advisable.

He can eliminate spending time and money on multiple visits to a number of specialists who, in turn, can then devote their valuable time to those cases which need the intensity of their specific knowledge.

Joseph P. Connolly, M.D.
J. A. Malerich, Jr., M.D.*
Mark J. Wegleitner, M.D.
West St. Paul, Minnesota

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*At the present time in the service of the United States.

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Cancer Family Syndrome

The Medical Genetics Section of the Department of Preventive Medicine and Public Health at Creighton University School of Medicine, Omaha, Nebraska, is interested in the study of patients showing an increased incidence of any histological variety of cancer in their families. Of particular interest to us is the cancer family syndrome, characterized by: (1) increased frequency of adenocarcinoma of all sites, particularly of the colon and endometrium, (2) early age at onset of cancer, (3) increased occurrences of multiple primary malignant neoplasms, and (4) autosomal dominant inheritance.

We are currently updating two large cancer families having the above characteristics who live primarily in the Midwest, in middle and northwestern Missouri, Iowa, Nebraska, Colorado, Michigan, Indiana, and Illinois. The initial phases of the investigations of the families have been published (Lynch, H. T., et al.: Hereditary Factors in Cancer; Study of Two Large Midwestern Kindreds, Arch Intern Med 117:206, 1966).

Physicians with patients known to have a familial cancer background may write to Henry T. Lynch, M.D., Associate Professor and Chairman, Department of Preventive Medicine and Public Health, Creighton University School of Medicine, 657 North 27th Street, Omaha, Nebraska 68131.

We invite your cooperation in our studies which will include a genealogical and medical investigation of the entire kindred in each case. All information obtained will be shared with family physicians in order to facilitate cancer control.

Special Article

The Doctor, His Emotions and His Heart

BARNEY M. DLIN, M.D.
Philadelphia, Pennsylvania

FROM TIME IMMEMORIAL, the heart has symbolized the care of the soul and the center of man's deepest emotions. Feared and respected, the heart is the organ of sudden death. The cardiovascular system is involved in the phenomenon of emotional life, especially in the expression of anxiety, the most common of all patient complaints. The emotions can alter pulse rate, stroke volume, cardiac output, blood pressure, blood clotting, blood shift, and blood chemistry. Little wonder, then, that passions and attitudes play a major role in the precipitation and aggravation of cardiovascular disease.

For over a century and a half occasional reports appeared in the literature delineating the connection between the emotions and coronary disease. In 1901 Sir William Osler stated that he believed emotion was the most common but least serious cause of angina pectoris. In describing the "coronary type," he pointed out: "It is not the delicate neurotic who is prone to angina, but the robust and vigorous in mind and body, the keen and ambitious man, the indicator of whose engine is always set at 'full speed ahead.' There is indeed a frame and facies at once suggestive of angina—the 'well-set man of from 45–55 years of age, with military bearing, iron-gray hair and florid complexion.'" Osler also commented on the high frequency of this affection among doctors, stating: "Yet, if hard work alone was responsible, would there not be a great many more cases? Everyone of these men (doctors) had an added factor—worry."

Emotional Factors

Anecdotal observations by astute clinicians are valuable; most are made on the acute effect of emotions in precipitating angina and/or sudden death. It was not until the middle of this century that systematic studies of the emotions and the heart were started.[18] Dunbar, in a psychiatric study of 22 patients, described a typical personality profile. Arlow also found a clear-cut constellation of personality traits in patients with coronary disease. Both found evidence for compulsive, competitive striving and concluded that the character structure of the patient predisposes to coronary occlusion. Dunbar referred to the "coronary personality" consisting of "compulsive striving, hard work, self-discipline and great need to get to the top." Both emphasized the psychodynamic importance of the patient's childhood conflicts with authority; Arlow described an early competitive relationship with a much feared and envied parent (usually the father). He states that the characteristic defense mechanisms used in dealing with this focal conflict were repression and identification, but that they served their purposes inadequately.

Environment

Master and Jaffe (1952), studying the factors in the onset of coronary occlusion and coronary insufficiency, amassed considerable evidence to show that coronary occlusion is not initiated by events in the external environment.

In a large series they found that about one half of the attacks began during sleep and rest, and since the majority of persons spend half the day this way "these activities may be considered coincidental."

Miles, Waldfogel, Barrabee, and Cobb (1954) could find no convincing evidence that the personality exhibited by the coronary patient, as compared to the control subject, could be implicated as a significant factor in the genesis of coronary artery atherosclerosis. They concluded that the similarities between the groups were more striking than were the differences. Miles et al. assumed that coronary occlusion can be precipitated by severe emotional stress but did not concern themselves with this question.

Social Pressures

In 1957 Weiss, Dlin, Rollin, Fischer and Bepler found little evidence to support the concept of a "coronary personality." Rather it seemed that the features attributed to a "coronary personality" might be personality characteristics influenced by cultural factors such as family emphasis on education, ascent in the social scale and material success. Focus of this study was to determine whether patients with coronary artery disease were more subject to emotional stresses prior to the occlusive episode than a matched group. Study of the personality and life situation of patients in an acute coronary occlusion group showed that gradually mounting tension of emotional origin, years or months in duration, occurred prior to the onset of the occlusion. Such tension was manifested by increased smoking and drinking, irritability, anger, insomnia, indecisiveness, social withdrawal and increased dependency on spouse, obsessive thinking, preoccupation with body symptoms, inability to concentrate, disturbances in memory, impotence, depression and fear. These tensions were primarily present in patients under 60 years of age.

A study[8] of 3500 men enrolled in a predictive study of clinical coronary heart disease revealed that certain emotional and environmental factors were dominant: a compulsive drive, aggressiveness and ambition, profound impatience, and immersion in multiple vocational and avocational pursuits fraught with self-imposed deadlines. These men were further noted to exhibit characteristic motor mannerisms in jaw and facial musculature, speech, and hands. Brum, Wolf and others[1,2,3] studied the social aspects of coronary heart disease in two adjacent, ethnically different communities. They found the more homogeneous and stable of the two communities was found to have a lower incidence of treated mental illness; they also noted, as have many others, that social and cultural factors influence the incidence of coronary heart and other diseases.

Heart Attacks—"The Doctor's Disease?"

Aside from Osler's mention of doctors' susceptibility to coronary disease, this area of investigation has remained almost unexplored; only a few[4,5,6,9,11,16,17] have ventured into this field. Perhaps this reluctance to involve ourselves in this area of study stems from personal attitudes.

Who among us has not been shaken by the sight or knowledge of one of our colleagues struck down by a heart attack? For days after, many of us slow down, smoke less, seem more concerned about caring for ourselves. Then, as the fears are denied or repressed, there is a gradual drift back to the increasing demands of work and, like the shoemaker with the shoeless children, we continue to neglect our own physical and mental welfare. Physicians are the great rationalizers and deniers, driven by the altruism of their calling.

The Young Physician

Startling observations[5,6] were made based on cold statistical data from the file of the American Medical Association. The average age of the active physician is 46 years. The young physician entering his profession at an average age of 25 has 43½ years of life ahead of him. In mid-life, at age 45, he may expect a further quarter century of lifetime. Almost 12 additional years remain to the average physician attaining age 65, a frequent age of retirement.

Young physicians have only a slightly greater expectation of life than white persons of the same ages in the general population, but this advantage, one fourth of a year, is lost even before middle mid-life. From age 30 on, the prospective lifetime for the physician is somewhat less than for white persons in the general population, but the differences are not significant. Diseases of the heart and coronary vessels account for 40.7% of the total deaths, far exceeding all other causes. If the recorded death rates from diseases of coronary arteries are considered alone, the ratio of the mortality of physicians to that of white males reaches the high figure of approximately 181%!

The authors conclude that this excess cannot be accounted for entirely by better diagnosis and certification of causes of death. They also suggest that causative factors may be operative though not immediately apparent. They further surmise that the *special activities and burdens of the profession*: the call to service at any time, the constant guard against varied infections, and the need for mental alertness, may well impose unique strains. Hence they recommend minimizing the stresses of the profession so that physicians may achieve the benefits which their favorable position makes possible. From a social and economic viewpoint the untimely death of a physician represents a serious waste because of the important service that is lost and because of the large investment involved in preparation.

General Practitioners

In a statistical study of British physicians between the ages of 35-64 years, Morris, Heady and Barley (1952) made the startling observation that the incidence of coronary disease in 1947-50 among general practitioners was almost twice as high as for all the rest of the profession. Using life-table methods and presuming that the present incidence will continue unchanged, the authors estimate that of 1000 practitioners, aged 35-45, some 20-25 will have a clinical attack of coronary disease before the age of 50; almost another 40 between ages 50-55, another 60 between ages 55-60, and a further 70 between ages 60-65. In other words, medical practitioners under 45 years of age who have not had symptoms of coronary heart disease have approximately a 20% chance of having an attack before age 65.

Other Specialists

From the analysis of 2587 questionnaires completed by physicians, Russek[15,16,17] found that in general practitioners coronary disease was three times more prevalent than in dermatologists and pathologists, thus confirming his thesis that *emotional stress of occupational origin* is one of the important etiologic factors in the genesis of coronary artery disease. Emotional stress of occupational origin may be far more significant than heredity, dietary fat, tobacco, obesity and physical exertion. At the time of the attack, 90% of the coronary subjects (as compared to 20% of the controls) were holding down two jobs, working more than 60 hours a week, or experiencing unusual fear, insecurity, discontent, frustration, restlessness or inadequacy in relation to employment. Extending his original physician survey, Russek compared physicians, dentists and lawyers engaged in general practice or in selected occupational specialties. General practitioners in each field showed coronary rates two to three times higher than those of specialists selected for study.

Testimonials To My "Heart" Attack

Most patients who have suffered from a coronary attack can put the finger on the cause. While recuperating from a heart attack in 1957, Lyndon Johnson told ranch callers that his attack began when he blew his top at an impertinent prying reporter.

Recently Dr. Irvin Page discussed his coronary attack. He recalls that events leading up to the fateful night had been particularly arduous; the turmoil of preparing for a meeting, the rush to the airport, the frustration and worry about plane service, etc. overshadowed the pains in his left chest. In spite of being slim, physically active, and moderate in food and tobacco, he admitted to having inner tensions which he outwardly disguised. Dr. Page now wisely recommends for himself the advice he has been giving his patients over the years. "Take the pressure off. Work at your own pace. Set your own priorities."

Methods of Control

Our approach to the study of patients suffering from acute myocardial infarction does not lend itself to classification according to personality types. More important is the emphasis upon the dynamic factors of personality and the setting in which the illness manifested.

Physicians with a cardiac disorder ordinarily are not referred for emotional help as frequently as non-physicians; they usually enter psychotherapy on their own initiative and for other reasons. In the course of treatment it may be discovered that there was a history of coronary occlusion which the physician has previously glossed over.

The physician is really no different from other human beings. The nature of his work causes him to formulate certain ideas about health, sickness and death and to develop special defenses to cope with the demands of work. He is subject to the same latent forces which affect any other human being.

The fact that the physician is twice as likely to have heart disease as a non-physician and the fact that the general practitioner stands three times the chance the specialist does indicates particular vulnerability related to problems of maladaptation; failure to adjust to the emotional demands of his work and the intrinsic conflicting forces therein.

Heart attacks do not just happen. In the majority of patients, increasing conflict and stress has been building up for months and years. Perhaps the patient was not aware of it, or if he was, he ignored it. No doubt his wife knew about it but felt helpless to do anything. When the attack comes, a significant percentage of patients recognize it as inevitable, accept it and make some kind of adjustment. The person who can't or won't is in trouble! Little wonder that the commonest complication of the heart attack among physicians is emotional! Laboratory and experimental evidence for emotional stress resulting in bodily changes is clear, but the ability to integrate our knowledge into effective medical practice is not as easily demonstrable.

Gradually Mounting Tensions

Significant Events

Significant events in the life of the individual usually occur approximately three years prior to the coronary insult. The great majority of these events involve unusual circumstances among persons in close relationship to the patient (e.g., losses or separation, death, serious illness or surgery) accompanied by emotional distress which forces him to make a major adjustment. Failure to do so results in symptoms.

Somatic Symptoms

About one year prior to the coronary episode, there appears a cluster of somatic symptoms—aches, pains, headaches, gastrointestinal distress, sexual difficulties, especially impotence, fatigue, insomnia, etc. with failure to adjust.

Some months before the coronary, further significant events involving the patient occur: e.g., an accident, terminating an affair, planning a big trip, reaching retirement, all endowed with a great deal of personal concern and identification, adding further insult to the patient. Such patients may develop cardiac phobias and fears, though repeated electrocardiograms indicate no evidence of cardiac involvement. There are commonly observed behavioral patterns indicating struggle, defense, submersion, or capitulation.

Games Doctors Play

The Conspiracy of Silence

Most examining physicians avoid the areas of inquiry which deal with emotional conflicts. Similarly, most patients keep their emotional conflicts to themselves for reasons of shame, embarrassment, guilt, etc. Thus, a non-verbal mutual conspiracy of silence is established. It is essential for the examining physician to provide the opportunity for the patient to speak about his personal conflicts and problems. He must listen and then offer judgments or solutions as to how the problems can be met. Most problems can be resolved in this manner; others will need psychiatric consultation for brief or prolonged therapy. Experience has demonstrated that the majority of emotionally-ill post-coronary patients, and especially physicians, need brief psychotherapy. Seldom do they get it!

Variable History

It is not uncommon for one patient to present three different histories to three different doctors, consciously or unconsciously slanted to suit the examining doctor; the variations depend upon who the listening physician is, what the patient feels the physician expects to hear, how hurried the interview is, what the circumstances are, etc.

The following three histories were taken from a physician patient by a medical resident, cardiologist, and psychiatrist respectively. In the first two histories, the patient made reference to nervous problems. Both examiners, however, avoided exploration in this area.

Case Histories

Case History: By Resident

C.C.: Myocardial infarction.

H.P.I.: "46-year-old white male physician in good health until two weeks ago when he noticed an elevation of blood pressure. *This caused him some anxiety* since this was a first occurrence. He then went on a cruise where he suffered some dyspnea. He didn't think much about this, but later had an electrocardiogram which showed some minor changes. He rested until return to port and was then admitted to hospital."

F.H.: Father died of myocardial infarction, rest negative.

Soc. Hist.: Smokes two to three cigarettes per day, rest negative. Remainder of history unremarkable.

Comments: This is a typical medical history given by a doctor patient who was not about to tell the resident anything except the "essential" medical data.

Case History: By Cardiac Consultant

"This 46-year-old physician states that, *aside from occasional nervousness* and a spell which he thought was due to heart disease in 1957, he regarded himself as well until two weeks prior to admission. Ten years ago he was conscious of an uneasiness in his left lateral chest wall. The uneasiness radiated to the precordial and midsternal regions. He suspected heart disease, saw his physician who took an electrocardiogram and reassured him. In recent months he has had *considerable emotional distress,* the nature of which he has not discussed with me.

Two weeks before admission he was *"pushing hard"* and under considerable tension, when he again felt queazy. He felt that his pulse was irregular. His blood pressure was 230/120. Frightened, he called his doctor. By the time the doctor arrived, the patient's pulse was regular and his blood pressure normal. Everything seemed fine and he was told that he might go on his vacation. At the resort he was quite upset, took his blood pressure almost every two hours. Because of shortness of breath, he saw a doctor where an electrocardiogram was taken. Repeat tracings were normal. The patient felt panicky. A cardiologist told him that his heart was normal. The patient then consulted his own doctor and was admitted to hospital upon return from vacation.

F.H.: Mother is well. Father died of infarction. Only sibling is well.

Soc. Hist.: Eight years ago stopped smoking, *but two months ago started in again because of his emotional tension."*

Comments: The patient provided a number of clues as to problems, including an initial "brush off" which the cardiologist responded to by noting significant tension—which he ignored.

Case History: By Psychiatrist

(Consultation requested by patient)

"Patient was a soft-spoken, gentle person lying calmly in bed surrounded by books, plants, television, radio, nurse, etc. He appeared relaxed and in full control of his emotions.

On my first visit he expressed fear of when the next attack would come. He had been thinking about the onset and was disturbed because he didn't recognize it. Lately he began to feel uncomfortable; he felt his tensions mounting and he was beginning to "think" again.

He stated that for the past year he had been sexually involved with a female patient, and although he has had many previous sexual affairs, this was the first which caused him so much turmoil. He noted feelings of tension, frustration, jealousy, suspicion, apprehension, excessive attachment, etc. He planned a trip to get away from this involvement, and it was in this setting that the feelings described in the history occurred.

Since he has been in the hospital recovering from his heart attack, he notes that he has been thinking of nurses in a sexual way. As he related this, he was visibly tense and shaky. His composure was gone. He stated that his father died while on his first day at work following his first coronary. The patient has been thinking more of his father while in the hospital. He notes also that there are similarities between himself and his father, including the dates and ages related to their respective coronary episodes. As the day of discharge approaches, the patient becomes increasingly anxious, fearing that he, too, may die on the first day back to work as did his father."

Comments: The above data was there for the asking; the clinician need only take the time to ask and listen.

The Doctor As Your Patient

As one physician said following his coronary, "Physicians, as a rule, are poor patients; they know too much and therefore never fully accept the guidance of a doctor as other sick people do. On the other hand, they are unable to approach their own case objectively; they are necessarily biased, and it is more difficult for them to adjust to a diseased condition." (Pinner and Miller . . . "When Doctors Are Patients.")

It has been clearly shown that the treatment received by a physician-patient usually differs from that given the lay-private patient. This may be particularly true of a physician with a coronary insult because the doctor in charge often fails to maintain his objective and empathic role. The patient has difficulty too, either hesitating about making demands on his medical colleague, knowing how overworked he is, or feeling compelled to prescribe for his own treatment by making suggestions and recommendations. For example, the question of a coronary angiogram was left up to the doctor-patient by a consulting cardiologist because the patient was also an astute clinician. "What a hell of a way to treat a patient!" said the doctor-patient.

Generally, physicians who are patients do not want to share the burden for diagnosis and treatment of their heart disease. They are too sick, too afraid, too concerned; they do not trust their own judgment and are not likely to take offense if the therapist does not consult with them on each procedure. But should they react with anger or hurt or resentment at being treated like any other patient, this reaction should be discussed candidly and viewed as a potentially serious obstacle to the doctor-patient relationship. The most reassuring thing that any physician can do for an ill colleague is to take charge. He and his family need the same kind of attention accorded any patient.

Remember the old saying, "The doctor who treats himself has a fool for a doctor and a fool for a patient."

Buckle Up

Many freeway accidents are caused by cars pulled off the road because of mechanical failure. If you plan to use a freeway on your next trip, prepare your car for continuous high speed driving conditions.

Before you go, brakes, exhaust system, windshield wipers and lights should be operating properly. Tires should be in good condition and properly inflated for continuous high speed travel. Fill the fuel tank and check water, fan belt, oil and battery.

On the road stop every two hours to have fuel, water, oil and tire condition checked. You will have to leave the freeway for these stops. Watch for signs indicating exits to service areas.

Learn what your gas gauge means. Know how much gas your tank holds when full, half full, etc. Know how many miles your car can go on a gallon of gas. Too many emergency stops on highways are due to running out of gas. Tire trouble is another of the most common causes.

Green Medicinals*

Herbs for the Liver

Ecclesiasticus said: The Lord hath created medicines out of the earth and a wise man will not abhor them.

Therapeutic herbs for the liver include bogbean, gooseberry, lilac, mandrake, snapdragon, and thistles. For anyone with a taste for gooseberries the following relish can be prepared.

Green Gooseberry Relish

Put into a preserving pan four quarts of green gooseberries, five pounds of brown or white sugar, and a little water. Boil until nearly cooked, then add another five pounds of sugar, a tablespoonful of powdered cloves, the same of powdered cinnamon, and a pint of vinegar, and boil till finished. It should boil three or four hours.*

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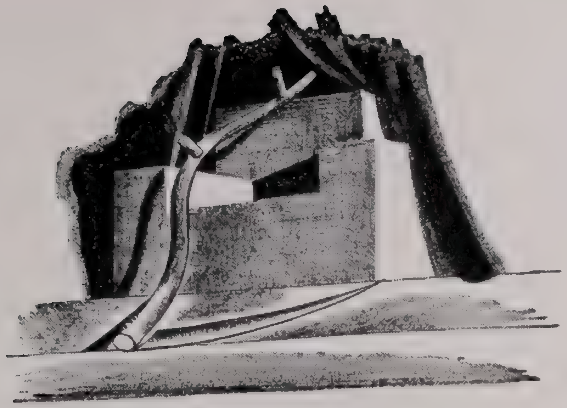
*C. F. Leyel: Green Medicine.



In Memoriam

Death is delightful. Death is dawn,
The waking from a weary night
Of fevers unto truth and light. —*Joaquin Miller*

EDMUND M. McLAUGHLIN, M.D.

Dr. Edmund M. McLaughlin, 91, one of the founders of the Winona Clinic, died November 28. Born in Owatonna, Minnesota, Dr. McLaughlin graduated from McGill University Medical School, Montreal, in 1903.

He was a fellow in the American College of Surgeons and a member of the American Medical Association and the Winona County Medical Society. He was a 50 Club and Life Member of the Minnesota State Medical Association.

Dr. McLaughlin is survived by his wife.

GEORGE E. FAHR, M.D.

Dr. George E. Fahr, 86, former medical chief at the Minneapolis General Hospital and head of the University of Minnesota Heart Clinic, died December 3. He had retired from both positions in 1950 but had kept active as a consultant and medical specialist at the Anoka State Hospital until six years ago.

Dr. Fahr was credited with introducing the electrocardiogram into wide use in this country.

He was born in Meadville, Pennsylvania, and graduated from the University of Chicago in 1904.

He is survived by his wife, a daughter and two sons.

RUSSEL EDWARD CARLSON, M.D.

Dr. Russel E. Carlson, 51, Stillwater physician, died November 16. He was born at Montrose and graduated from the University of Minnesota Medical School in 1939.

He was a member of the Washington County Medical Society and had been president of that society in 1955 and 1958. Dr. Carlson was a former member of the Professional Liability Committee of the Minnesota State Medical Association and had served as a delegate to that Association from 1959 through 1966. He was a member of the American Medical Association.

Dr. Carlson is survived by his wife, one son and five daughters. Dr. Vernon Carlson of Buffalo, Minnesota, is his brother.

THOMAS MOE, M.D.

Dr. Thomas Moe, 75, Moose Lake physician, died October 27. Born in St. Paul, Dr. Moe graduated from the University of Minnesota Medical School in 1924. In 1925 he and Mrs. Moe moved to Moose Lake where he took over the operation of the Moose Lake Community Hospital. Dr. Moe had been a surgeon and physician for the Moose Lake area for the past 43 years.

He was a member of the St. Louis County Medical Society and the American Medical Association and a Life Member of the Minnesota State Medical Association.

Dr. Moe is survived by one daughter and two sons.

HENRY E. BINET, M.D.

Dr. Henry E. Binet, 79, Grand Rapids retired physician and surgeon, died November 13. He had lived in Grand Rapids 52 years. Born in Marquette, Michigan, Dr. Binet attended the Northwestern University Medical College.

He was a fellow of the American College of Physicians and Surgeons, member of the Range Medical Society, former member of the Itasca County Hospital and Welfare Board, member of the American Medical Association and an Associate and 50 Club Member of the Minnesota State Medical Association.

Dr. Binet helped establish and build an occupational therapy pavilion at the Itasca County Nursing Home and a nursing home chapel which is named after him.

He is survived by his wife, a daughter and a son.

GEORGE I. BADEAUX, M.D.

Dr. George I. Badeaux, 80, Brainerd surgeon, died October 29. Born in Brainerd, Dr. Badeaux was a lifetime resident.

For many years he served as secretary of the Upper Mississippi Medical Society, was a fellow in the American College of Surgeons, Member of the American Medical Association and a 50 Club and Life Member of the Minnesota State Medical Association.

He is survived by his wife and three sons.

LEONARD M. LARSON, M.D.

Dr. Leonard M. Larson, 72, tuberculosis specialist, died October 19. Born in Minneapolis, Dr. Larson received his medical degree from the University of Minnesota Medical School.

He was a member of the Hennepin County Medical Society and the American Medical Association and an Associate Member of the Minnesota State Medical Association.

He is survived by his son and a daughter.

FRANCIS J. LEPAK, M.D.

Dr. Francis J. Lepak, Duluth physician for nearly 60 years, died January 6. He was 86. Born in Gnesen Township, he was a graduate of the Northwestern University Medical School.

Dr. Lepak was a member of the St. Louis County Medical Society, the American Society of General Practitioners and the American Medical Association. He was a 50 Club and Life Member of the Minnesota State Medical Association. He was on the staff of St. Mary's, St. Luke's and Miller hospitals.

He is survived by three sons.

E. LAWRENCE MEYER, M.D.

Dr. E. Lawrence Meyer, 86, well-known Minneapolis physician, died July 2. Born in St. Louis, Missouri, Dr. Meyer attended the University of Minnesota Medical School where he obtained his medical degree in 1905.

He was a member of the Hennepin County Medical Society and the American Medical Association and a 50 Club and Life Member of the Minnesota State Medical Association.

He is survived by his four grandchildren.

JOSEPH E. HALPIN, M.D.

Dr. Joseph E. Halpin, 63, Rush City physician, died January 1. Born in Alma Center, Wisconsin, Dr. Halpin graduated from the Marquette University Medical School. He came to Rush City in 1930 and practiced medicine there until his death.

He was a member of the East Central Minnesota Medical Society, the Minnesota State Medical Association and the American Medical Association.

Dr. Halpin is survived by his wife and two sons.

WALLACE A. GLEASON, M.D.

Dr. Wallace A. Gleason, St. Paul surgeon, died December 26. Born in Hillsboro, North Dakota, Dr. Gleason attended and graduated from the University of Minnesota Medical School.

He was a member of the Ramsey County Medical Society, the Minnesota State Medical Association and the American Medical Association.

Dr. Gleason is survived by his wife and three sons.

After the Winter . . . God Sends the Spring

Springtime is a season
Of Hope and Joy and Cheer,
There's beauty all around us
To See and touch and hear . . .
So, no matter how downhearted
And discouraged we may be,
New Hope is born when we behold
Leaves budding on a tree . . .
Or when we see a timid flower
Push through the frozen sod
And open wide in glad surprise
Its petaled eyes to God . . .
For this is just God saying—
"Lift up your eyes to Me,
And the bleakness of your spirit,
Like the budding springtime tree,
Will lose its wintry darkness
And your heavy heart will sing"—
For God never sends The Winter
Without the Joy of Spring.

Helen S. Rice

Meetings and Announcements

There is no great concurrence between learning and wisdom.—Francis Bacon.

FEBRUARY

Scott-Carver County Medical Society, Regular Meeting, Wagner's Supper Club, Jordan, 6:30 P.M., February 4.

Minnesota Academy of Medicine, Town & County Club, St. Paul, 6 P.M., February 12.

Minnesota Academy of Ophthalmology & Otolaryngology. Regular Meeting, Minneapolis Athletic Club, Dinner, 7 P.M., Meeting 8 P.M., February 14.

Minnesota Radiological Society. Winter Meeting—Symposium on Coronary Arteriography, Sheraton-Ritz Hotel, Minneapolis, February 15.

Blue Earth Valley Medical Society. Regular Meeting, Interlaken Golf Club, Fairmont, 7 P.M., February 19.

McLeod County Medical Society. Regular Meeting, 6:30 P.M., February 20. Location to be announced.

Freeborn County Medical Society. Dinner Meeting, 7 P.M., February 20. Location to be announced.

Stearns-Benton County Medical Society. Annual Business Meeting, The HUB, Waite Park, 6:30 P.M., February 20.

Twin City Urological Society. Town & Country Club, St. Paul, 6 P.M., February 21.

Symposium on Management of Your Diabetic Patient. Diabetes Detection Center, 916 E. 15th St., Minneapolis, February 22.

Waseca County Medical Society. Regular Meeting, Waseca Memorial Hospital, 6:30 P.M., February 24.

BlueEarth County Medical Society Meeting, Century Club, 7 P.M., February 24.

American Academy of Occupational Medicine (Annual Meeting), Sheraton Plaza Hotel, Boston, February 5-7. Contact Bertram D. Dinman, M.D., Institute of Industrial Medicine, The University of Michigan Medical Center—W5634, Ann Arbor, Mich. 48104.

American College of Cardiology, [E], New York Hilton, New York, February 26-March 2. Contact William D. Nelligan, 9650 Rockville Pike, Bethesda, Md. 20014.

American College of Radiology, [M], Regency Hyatt House, Atlanta, February 18-22. Contact William C. Stronach, LL.B, The American College of Radiology, 20 N. Wacker Dr., Chicago.

American College of Surgeons (18th), Puerto Rico Chapter, San Juan, PR, February 25-March 1. Contact Ramón Isales, M.D., 730 Ponce de Leon, Hato Rey, PR 00918.

American College of Surgeons, Sectional Meeting, Sheraton-Fontenelle Hotel, Omaha, February 3-5. Contact Communications Division, American College of Surgeons, 55 E. Erie St., Chicago 60611.

Thirty-Second Annual Meeting
The New Orleans Graduate Medical Assembly

The thirty-second annual meeting of The New Orleans Graduate Medical Assembly will be held March 10, 11, 12, 13, 1969, headquarters at The Roosevelt Hotel.

Nineteen outstanding guest speakers will participate and their presentations will be of interest to both specialists and general practitioners. The program will include fifty informative discussions on many topics of current medical interest, in addition to a clinicopathologic conference, medical motion pictures, round-table luncheons, and technical exhibits. This program is acceptable for three and one-half (3½) prescribed hours and twenty-eight (28) elective hours by the American Academy of General Practice. An interesting and enjoyable program of entertainment for visiting ladies has been planned.

Electroencephalography Course

A course in Current Problems in Electroencephalography: Advances toward their Solution; Date: March 13-15, 1969, Place: Houston, Texas. Sponsors: The American Electroencephalographic Society and Baylor University College of Medicine. For further information contact: Dr. Peter Kellaway, Baylor University College of Medicine, Texas Medical Center, Houston, Texas 77025.

(Continued from page 349)

ST. PAUL: Spacious suite in new split-level building, partitioned for medical offices. Other level occupied by dentist. Excellent location adjacent to large shopping center. 1504 White Bear Avenue, 774-7144.

Oxboro Medical Clinic for sale in Bloomington, Minnesota's third largest city. Earn attractive return while current lease expires in four years. Clinic comfortably houses 11 doctors, each with 3½ examination rooms. Central air conditioning, adequate parking, and much more. Contact Towle Real Estate Co., 333-2445, Area Code 612.

GENERAL PRACTITIONER WANTED: To associate with Physician-Surgeon in Owatonna, a Southern Minnesota community, 25,000 population. Clinic building 3 years old; with five large treatment rooms; lab; x-ray; central supply; two doctors' offices; pharmacy; and business offices. Located next door to 85 bed City Hospital. Good opportunity for partnership. Contact: O. W. Roberts, M.D., 920 South Cedar Street, Owatonna, Minnesota. Phone 451-4630.

EXPERIENCED GENERAL PRACTITIONER: Available for Locum Tenens. One or two week periods. After April 1st. Solo practice preferred. Write Minnesota Medicine 385, 375 Jackson, St. Paul, Minn. 55101.

RESIDENTS IN PSYCHIATRY: Vacancies for July 1, 1969. Three years approved eclectic residency program with emphasis on community psychiatry, milieu, individual and group therapy. 350 inpatients; large outpatient dept.; children's unit; excellent senior staff; affiliation with University of Iowa. Stipend $15,000 for residents with Iowa license or immediate eligibility for regular license. Stipend for foreign graduates who must have ECFMG, $12,240. Federal stipend available to physicians with four years non-psychiatric training or experience following internship amounting to $15,000 annually, of which $3600 is tax exempt. Enthusiastic and dynamic training and treatment programs that are best understood by a personal visit. Write or call W. C. Brinegar, M.D., Supt., or William Blyth, M.D., Mental Health Institute, Cherokee, Iowa.

NINETEEN-MAN Wisconsin group located in college community of 40,000 with excellent hospital facilities is seeking additional associates in the following areas: (1) Internal Medicine, (2) General Practice, (3) Pediatrics and (4) Orthopedics. For further information please contact D. R. Griffith, M.D., Midelfort Clinic, Eau Claire, Wisconsin 54701.

GENERAL PRACTICE AVAILABLE. Retiring because of age. Fine clientele. Progressive town of 50,000 with large referral area. Excellent Hospital and University facilities. Air conditioned offices in good location. Contact T. Q. Benson, M.D., 1524 Walnut Street, Grand Forks, N. D.

INTERNIST: Board certified or eligible. 269-bed General Medical and Surgical Hospital in Michigan's Upper Peninsula. Licensure any state, salary dependent upon background and qualifications. Excellent benefits for retirement, vacations, sick leave, and professional improvements. Non-discrimination in employment. Contact Chief of Staff, VA Hospital, Iron Mountain, Michigan 49801.

SECOND GENERAL SURGEON needed by busy twelve man specialty group in attractive Minnesota community of 15,000; unique industrial, business and recreational center close to the Twin Cities; ideal family environment with all cultural and recreational facilities available; new clinic and new hospital; weekend coverage assured; terms negotiable; paid interview. Write or call collect: Administrator, The Interstate Medical Center, P.A., Red Wing, Minn. Tel. No. 388-3503.

OB-GYN—Join group of 4 GP's. Immediate work load: Time off assured. Early partnership opportunity. Well equipped clinic, established in 1962, recently expanded, in growing community of 7,000, 30 minutes from downtown Minneapolis-St. Paul. Fully accredited 116 bed hospital in community. Call or write J. E. Ponterio, M D. (612) 445-1305.

PROFESSIONAL OFFICE SPACE over 500 or 1000 sq. ft. carpeted, paneled, new dec. in new bldg. Hwy. #13 & 35 W., Burnsville. Doctors urgently needed for this area. reas. rent. Tel. 454-1233.

Physicians mend or end us; but though in health we sneer, when sick we call them to attend us, without the least propensity to jeer.—Lord Byron

A human being is an ingenious assembly of portable plumbing.—Chrisopher Morley.

A conservative is a man who just sits and thinks, mostly sits.—Woodrow Wilson.

Minnesota Medicine at a Glance

The Anatomy of the Facial Nerve—*Kullmann and Cody* Page 213

The makeup and distribution of the facial nerve is described.

Abdominal Aortic Aneurysm—*Gambill* Page 227

There have been many cases reported in which an abdominal aortic aneurysm has ruptured into the duodenum with fatal results. The present case exhibits features which made the true diagnosis obscure even to experienced physicians. The pain was slowly progressive and confined to the lower abdomen. There was consistent loss of weight and strength suggesting malignancy. Confirmatory laboratory tests of pancreatic malignancy were present. If the patient had not elected to defer exploration, perhaps the outcome would have been happier.

Open Heart Surgery—*Kiser et al.* Page 231

Four patients with an average age of 75 are presented who successfully underwent open heart valvular surgery.

Three Basic Brain Models—*Buckley* Page 235

The phylogenetic development of the primate nervous system basically involved the integration of three brains: (1) the reptile brain; (2) the early mammalian or visceral brain; and (3) the primate brain or neocortex. The author traces the historical appearance of three conceptual brain models that led to a more complete understanding of the functioning of the primate central nervous system including the mind.

Pernicious Anemia in North American Indians—*Olin and Harrington* Page 243

Two cases of pernicious anemia in North American Indians of mixed parentage are reported from the Fargo Clinic and Neuropsychiatric Institute. The disease is rare among among Indians, Eskimos, and Orientals. The authors found no previous cases reported and believe the disease among Indians is inherited from admixture of genes from Caucasians.

Acute Neurological Deterioration Following Lumbar Puncture—*Long et al.* Page 247

The necessity of a diagnostic test is measured principally by whether its results will affect the plan for investigation or treatment of a patient. The authors re-emphasize the importance of this rule in the use of lumbar puncture by citing six cases in which adverse side effects followed this procedure when it was employed ill-advisedly. The conditions under which it may be required and the precautions that should be observed are discussed.

The Doctor, His Emotions and His Heart—*Dlin* Page 369

Dr. Dlin calls our attention to the increased incidence of cardiac disorders among physicians. His suggestions for re-orienting our schedules, work obligations, etc., are timely, as are also his suggestions for the physician who cares for a colleague with a cardiac insult.

A M A C

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STATE MEDICAL ASSOCIATION

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MARCH, 1969

Special Issue

Wilford Hall USAF Hospital
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For the "Cheater Eater"

Formulas: Each 'Dexamyl' *Spansule* capsule No. 1 contains 10 mg. of Dexedrine® (brand of dextroamphetamine sulfate) and 1 gr. of amobarbital, derivative of barbituric acid (Warning, may be habit forming). Each 'Dexamyl' *Spansule* capsule No. 2 contains 15 mg. of Dexedrine (brand of dextroamphetamine sulfate) and 1½ gr. of amobarbital (Warning, may be habit forming).
Before prescribing, see complete prescribing information in SK&F literature or *PDR*.
Contraindications: Hyperexcitability, undue restlessness, hyperthyroidism, porphyria; in patients on MAO inhibitors.
Precautions: Use with caution in patients hypersensitive to sympathomimetics or barbiturates and in coronary or cardiovascular disease or severe hypertension. Excessive use of the amphetamines by unstable individuals may result in a psychological dependence. Rarely, symptoms of toxic psychosis (hallucinations, confusion, panic states, etc.) may occur with amphetamines, usually after prolonged high dosage. In these instances, withdraw the medication. Use cautiously in pregnant patients, especially in the first trimester.
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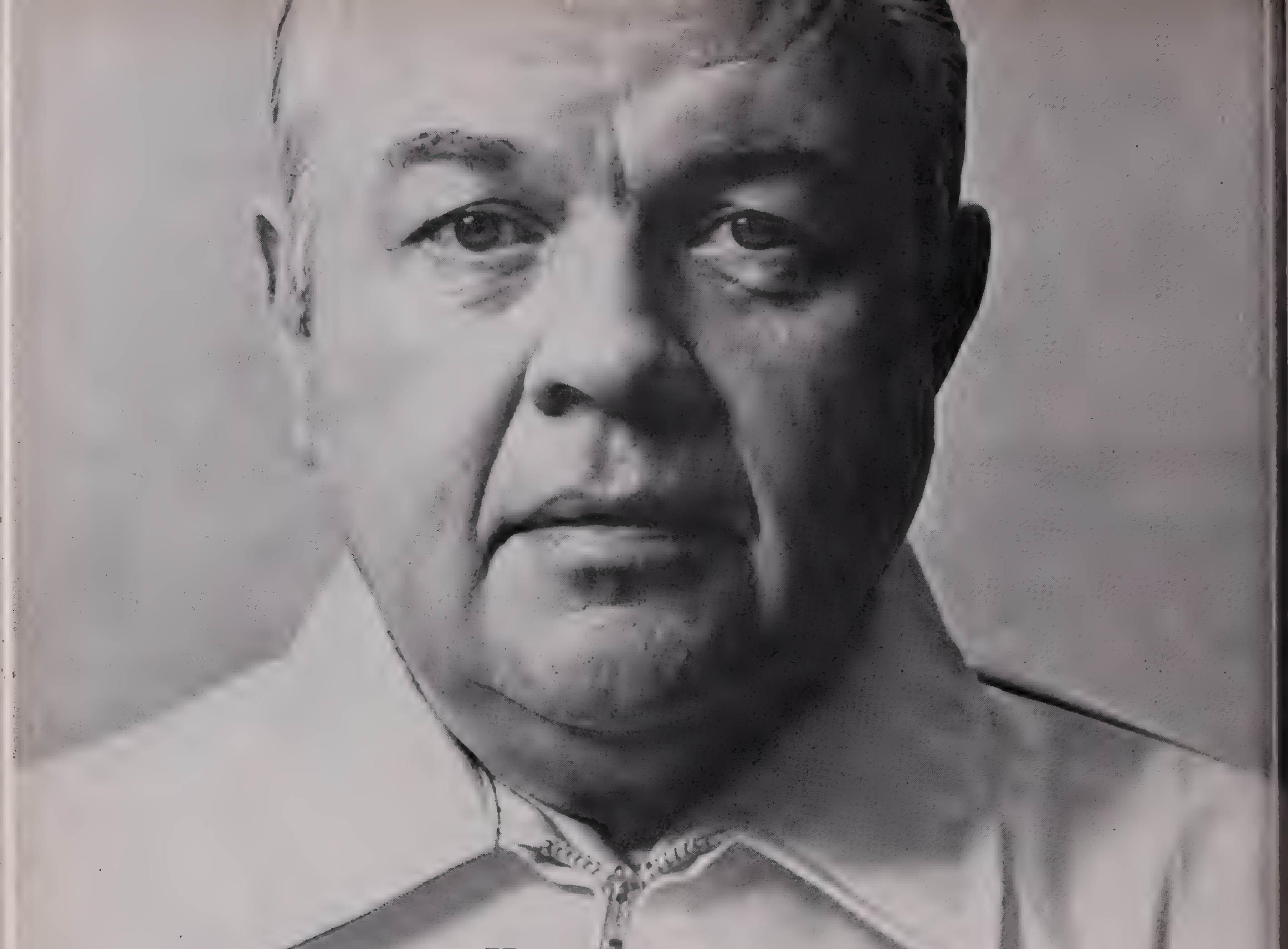

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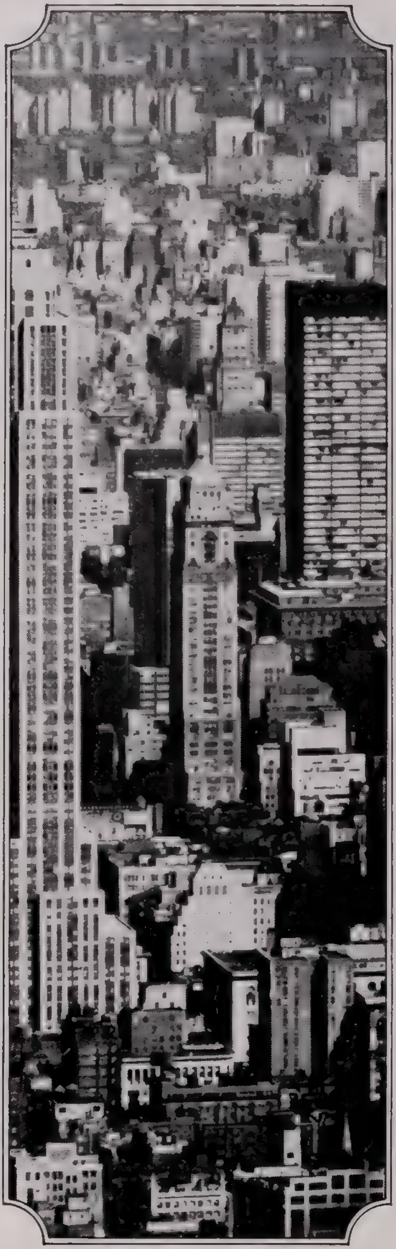

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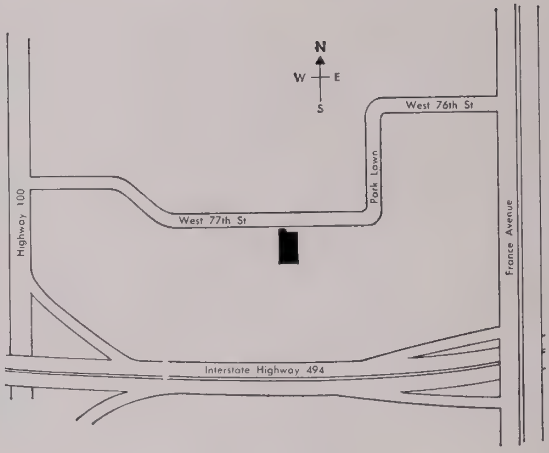
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"The skill of the physician shall lift up his head and in the sight of great men he shall be in admiration." (Ecclesiasticus 38:3)

THE PHYSICIAN can take pride in his lineage. Stone Age surgeons set fractures and with their flint tools, amputated digits and extremities and trepanned skulls (to release demons). Ancient Egypt had physicians for various parts of the body. Outstanding physicians were deified—in Egypt, Imhotep, and in Greece, Aesculapius (who sired daughters Hygeia and Panacea and was surgeon-in-chief of the Argonauts in search of the golden fleece). Hippocrates (460 B.C.) treated dislocations of the hip, shoulder and jaw. Celsus (14 A.D.) has been called the father of plastic surgery; his De Re Medicina was one of the first printed medical books, and that in 1478.

Claudius Galen (born in Greece about 130 A.D.) was outstanding in his day and for fifteen centuries thereafter. Not without conceit, he credited Hippocrates but stated, "His knowledge in some subjects is not sufficiently extensive; he is often obscure after the manner of the ancients; in order to be concise, he opened the road, but I have rendered it passable." It was said, "Galen was the last of the Greeks and when he spoke no more, the voice of the ancient world was hushed. Galen was the final star that shone in the twilight of antiquity, and when his effulgence was extinguished, there settled over Europe a darkness that was not lifted for many centuries."

Limitations of time and space permit mention of only a few of the great physicians. Herophilus (anatomy) and Erasistratus (physiology) publicly dissected live condemned criminals. Dioscorides was an army surgeon in the service of Nero—a great botanist, he praised the merits of opium. Abu Bekr Mohammed el-Razi (Rhazes, 865-925), a Persian, performed tracheotomies, set fractures, used animal gut sutures, and founded many hospitals. Ibn Sina (Avicenna, 980-1037), also Persian, was to the Moslems what Galen was to the Romans. From the great medical school in Salerno (established by Benedictine monks on the advice of Arab physicians) came the Regimen Sanitatis Salerni (presumably authored by John of Milan). Incidentally, this was a base hospital for the Crusaders.

John of Murfield (England—late 1300's) is remembered for the couplet:

> "When Physick's dearly bought, it doth much healing bring,
> But when 'tis freely given, 'tis ne-er a useful thing."

Ambroise Paré (1510-1590) "restored surgery to a worthy place." John Hunter (1728-1793) was an outstanding English Army and Naval surgeon. Corvisart (1755-1821) was physician-in-ordinary to Napoleon. Joseph Lister (1827-1912) made surgery safe. Crawford Long introduced ether (1842) and James Young Simpson chloroform (1847); Oliver Wendell Holmes coined the term anaesthesia.

Guy deChauliac (14th century), sometimes called the father of modern surgery, wrote in his Chirurgia Magna:

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Precautions: Use cautiously, if at all, in a patient with a strongly positive history of allergy.

In prolonged therapy with penicillin, and particularly with high parenteral dosage schedules, frequent evaluation of the renal and hematopoietic systems is recommended.

In suspected staphylococcus infections, proper laboratory studies (including sensitivity tests) should be performed.

The use of penicillin may be associated with the overgrowth of penicillin-insensitive organisms. In such cases, discontinue administration and take appropriate measures.

Adverse Reactions: Although serious allergic reactions are much less common with oral penicillin than with intramuscular forms, manifestations of penicillin allergy may occur.

Penicillin is a substance of low toxicity, but it possesses a significant index of sensitization. The following hypersensitivity reactions have been reported: skin rashes ranging from maculopapular eruptions to exfoliative dermatitis; urticaria; and reactions resembling serum sickness, including chills, fever, edema, arthralgia, and prostration. Severe and often fatal anaphylaxis has occurred (*see* Warnings). Hemolytic anemia, leukopenia, thrombocytopenia, and nephropathy are rarely observed side-effects and are usually associated with high parenteral dosage.

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Anterior Spinal Fusion

PAUL W. MYERS, Colonel, USAF, MC*

"THE NOVELTY OF A METHOD naturally leads to the enthusiasm of its exponents, and the claims which are first put forward need to be tempered by the experience gained with time.[11]† With this consideration in mind, our experience with the anterior fusion operation is presented.

Indications

The anterior approach to vertebral bodies and intervertebral discs, as well as to the cervical canal and its contents, has become the established method for managing the following conditions: (1) drainage of paravertebral cervical abscesses, and (2) removal of partially destroyed bodies caused by malignancies, intradural extramedullary anterior extensions of benign neoplasms, crushed or comminuted vertebral bodies caused by trauma, damaged discs caused by trauma, central disc fragments, posterior spondylotic ridges compromising the canal, osteophytes compromising nerve root takeoff, and soft lateral fragments.

No current operative method constitutes a less morbid approach to the anterior cord surface and those structures lying anterior to it than the anterior operation. Some surgeons have advocated the anterior route for cervical cordotomy also, but our experience with this operation is limited.

The soft lateral extruded disc can be removed easily by an anterior or a posterior approach. There are proponents of each technique, and no valid argument can be made for either method because both are equally effective.

The indications and problems attendant on the anterior approach in the cervical region are identified as the result of a study of the first 213 of 297 patients seen between November 2,

---

*From the Neurosurgery Service, Department of Surgery, Wilford Hall USAF Hospital, Lackland Air Force Base, Texas.

†Bowsher, D.: Cerebrospinal Fluid Dynamics in Health and Disease, American Lecture Series, Springfield, Ill.: Charles C. Thomas, Publisher, p. 8, 1960.

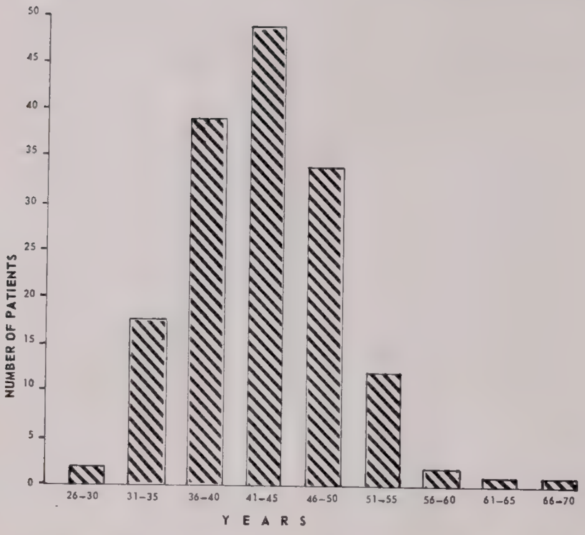

Fig. 1—Distribution of patients by age.

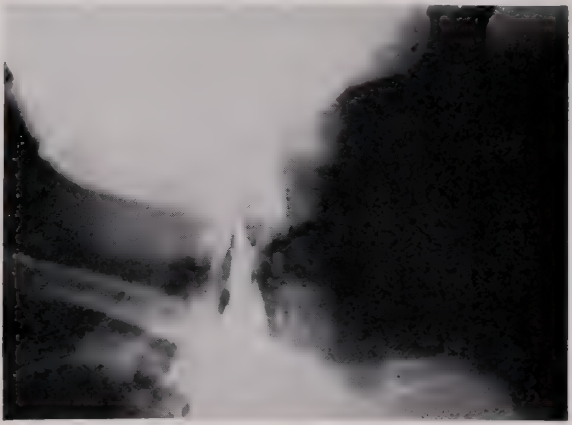

Fig. 2—Oblique view, myelogram of soft lateral disc. (Soft fragment C6/7)

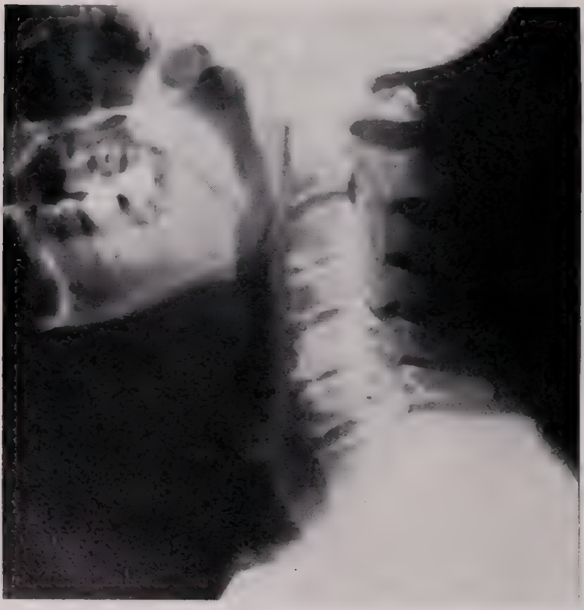

Fig. 3—Spondylosis C5/6, preoperative lateral view.

1961, and July 1, 1968. The most recent 84 patients, seen between July 1, 1967, and July 1, 1968, have not been followed long enough for an adequate evaluation. However, reference will be made to the technique used in some of the later patients.

This paper will discuss only three indications for anterior spinal fusion: (1) relief of root compression caused by "hard" or "soft" discs, (2) myelopathy produced by spondylotic bars, and (3) management of fractures and/or fracture-dislocations. The management of complications encountered will be described. The other indications for the procedure will become the basis for a later paper.

Cervical Disc Disease

Like that of other investigators, our experience indicates that patients with nerve root compromise present fairly typical clinical findings, consisting of neck and/or shoulder pain, radiating arm pain, and extension of that pain to certain finger groups.

Localization Not Specific

Paresthesia of the digits is common, but localization of this complaint is of no value. Fifty-nine of the 158 patients in this group with disease clearly confined to one level noted radiation of pain, paresthesias or numbness to some fingers. Twenty-four patients noted involvement of the thumb and index finger when the level affected was C5/6, and 21 had the same distribution with the disease at C6/7. Five with disease at C5/6 and nine with disease at C6/7 noted problems in the fourth and fifth fingers.

Muscle Weakness

Muscle weakness is of greater localizing value. When the deltoid, shoulder abductors, pectoralis major, or biceps are weak, the problem is invariably at C5/6, but on rare occasions it may be at C4/5. Weakness of the triceps indicates that the C6/7 level is affected. The rapidity of onset of arm weakness has attracted our attention, for it can become extensive within a few hours. Absence of diminution of reflex is supportive. The distribution by sex in the present series of patients is 135 males and 23 females. The distribution by age is shown in Figure 1.

Hard vs. Soft Discs

Cervical disc disease of the hard or soft type is a disease of the middle decades, as the age distribution reveals. If a patient has spondylosis but remains asymptomatic until he is 50 years of age, most likely he will have no difficulty unless he is involved in a traumatic episode.

Myelography has localized the disorder accurately in 157 of the 158 patients; only one had an unsuccessful myelogram. In the few instances when discography was used, it has served to correlate the myelographic findings and has been done at time of operation.

The 158 patients studied have had a combination of both soft and hard disc problems. One fourth of these (38 patients) known to have spondylosis also had free fragments. Identification of fragments can be facilitated by injection of indigo carmine into the disc prior to cleaning out the interspace. These fragments have been over and under the root primarily in the axilla, but some out toward the foramen (Figures 2 through 7).

One-hundred and sixty fusion operations have been done on 158 patients (Table 1). Two patients have been fused at two different levels on separate occasions. Eleven (6 percent) had been operated previously by the posterior approach. One patient had been operated at another clinic and two previously

TABLE I
Total Cases by Fusion Levels

No. of Levels	No. of Fusion Operations
One	
C4/5	3
C5/6	49
C6/7	44
C7/1	1
Two	
C4/5/6	6
C5/6/7	46
Three	
C3/4/5/6	1
C4/5/6/7	8
Four	
C3/4/5/6/7	2
Total	160

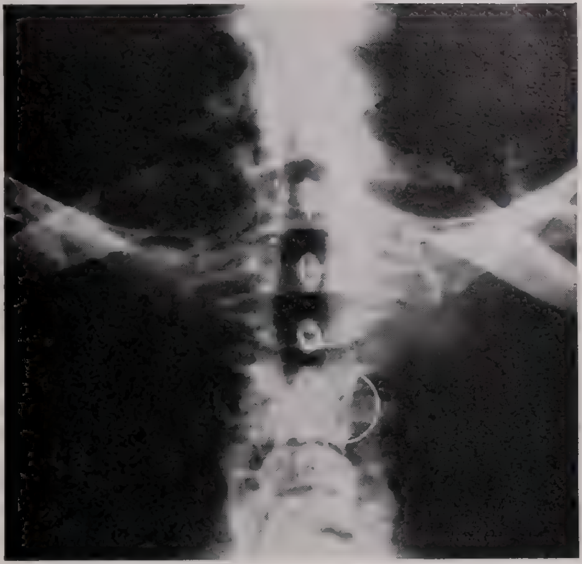

Fig. 4—Spondylosis, preoperative anteroposterior view. Note spurs.

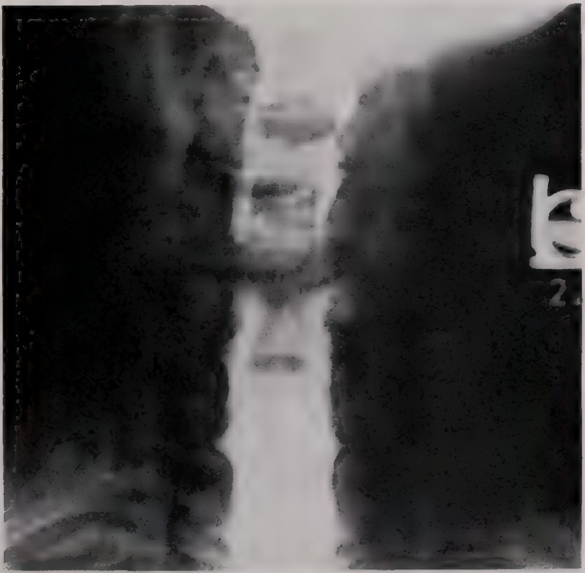

Fig. 5—Anteroposterior myelogram of spondylosis.

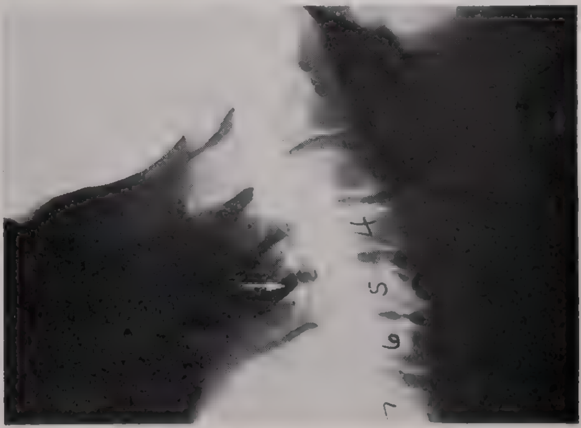

Fig. 6—Lateral myelogram of spondylosis.

at this hospital, including one operated twice within ten days. It is significant to note that nine had recurrent symptoms of the same type in the same arm and that seven have had this recurrence in less than two years. The intervals in four patients have been nine, four, three and three years, respectively; two have had their symptoms in the contralateral extremity.

Single level fusions have been done on four at the same level of the posterior approach, (i.e., the same root), and all of them had shown myelographic defects originally. Five patients with initial single level disease have been found to have additional adjacent level defects on a later myelogram. Two-level fusions have been done; these patients have had complete relief. One patient, with a C6/7 block and extensive multiple level disease, had been decompressed from behind at the myelographic block level and one higher, but failed to obtain relief. Six weeks later a three-level fusion was done; the patient became symptom-free. One patient who had had two levels operated from behind returned four years later with the same complaint and the same findings. A repeat myelogram disclosed defects at three levels (C4/5/6/7). A three-level fusion has afforded only minimal relief; however, he is working. There has been no return of intrinsic muscle bulk in the hands.

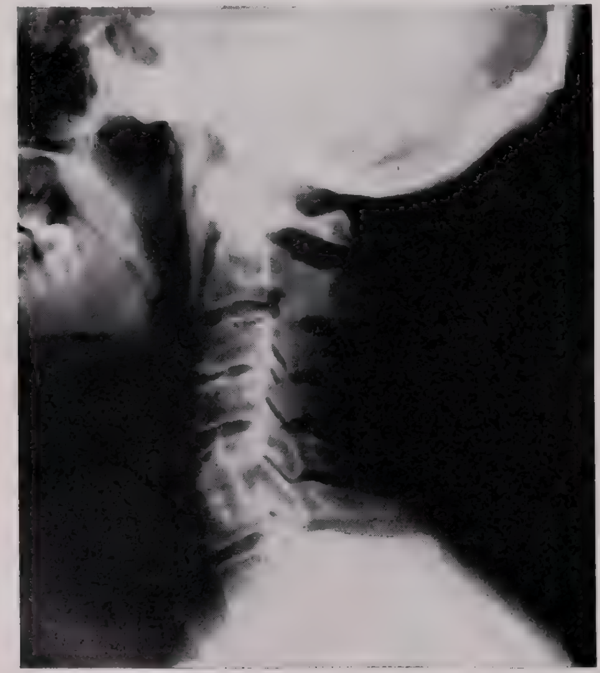

Fig. 7—Spondylosis, postoperative.

Experience with fusion operations indicates that 10 of the 11 patients have had relief of arm and shoulder pain, paresthesias and weakness (Table 2). In addition, one patient who had had a previous anterior fusion at C5/6 elsewhere had recurrent symptoms three months later. Operation after a myelogram showing a C6/7 defect has resulted in removal of a large fragment. Two patients operated at this hospital have required re-operation at another level three years and ten days later, respectively. Re-operation in one patient has been performed because of persistence of severe pain along the medial scapular border, and another adjacent level fused; no free fragment had been overlooked. The patient had gained relief eventually, when osteomyelitis caused a loss of the graft. This patient is discussed under Complications.

Observations on Procedure

Performing anterior fusions in the hard and soft disc group has given an indication of what results can be expected. (1) Vigorous work about the C6 root often produces permanent numbness of the tip of the thumb. (2) Return of the reflex is unpredictable; if it does return, this will occur within 30 days. (3) Atrophy and/or weakness of the intrinsic muscles of the hand may not improve, but gradually worsen. (4) The majority of the patients have immediate relief of pain. (5) Return of shoulder and arm strength is usually rapid, but it is difficult in some patients to determine whether this return of strength is based solely on relief of pain. (6) One of the most common early complaints in this disease is pain along the medial scapular border; for lack of a better term, this well localized area of pain has been labeled "Myer's Point." (7) In patients who have extensive arm weakness and atrophy, improvements are seen as early as three months postoperatively. (8) Removal of free fragments by a laminectomy does not guarantee relief of pain if associated spurs are present. (9) Marked angulation at the graft site occurs infrequently but does not seem to alter the results. (10) Numbness of all fingers indicates both C6 and C7 root compression. (11) Free fragments usually are found when the posterior longitudinal ligament has been torn spontaneously. (12) Any bone used for fusion other than autogenous iliac crest is more likely to prolong the development of a solid fusion.

Incision

Many surgeons on the staff of the Neurosurgery Service have performed the anterior fusion operation, but technique has varied little. If a one-level or two-level fusion is to be performed, the lateral transverse incision on the right side of the anterior neck seems to be efficacious, for two levels can be reached with ease through this approach. If the fusion requires more than two levels, an incision is made along the medial border of the sternocleidomastoid similar to that used for exposure of the carotid artery. The incision can be lengthened in either direction, and several levels can be done with ease. It is important not to be too vigorous with an inferior dissection at the depths of the wound, because recurrent laryngeal nerve palsies have occurred with exuberant traction.

Identification of Interspace

The attack on the interspace begins with radiographic identification. A needle is inserted into the interspace and a cross-table film taken. When the proper space has been identified, indigo carmine is injected in order to identify readily any free disc fragments from the coloring of the material. The Hall air drill has been used more extensively in order to obtain a symmetrical opening between the vertebral bodies.

Removal of Material

Then curettes are taken to remove the disc material. Transverse bars are curetted away, or a Cloward punch is used. The posterior longitudinal ligament is removed when ridges or osteophytes are present. In patients who have relatively acute soft disc disease, the posterior longitudinal ligament is usually disrupted, and if so, it is removed. The standard Cloward instrument is used to remove the iliac bone dowel. Our experience has indicated that when doing more than one level, the dowels cannot "kiss" one another, for, if this occurs, angulation will develop. Use of the Hall drill permits extremely accurate placement of the hole. Angulation can be prevented by allowing plenty of good cervical body to remain between the grafts.

TABLE 2

Previous Posterior Laminectomies

Case number	6	41	45	56*	63	75	77†	108‡	131	184	205
Level previous myelogram defect	6/7	6/7	5/6	Block 6/7	6/7	6/7	5/6/7	6/7	5/6	5/6	5/6
Level of posterior approach	6/7	6/7	5/6	5/6/7	6/7	6/7	5/6/7	6/7	5/6	5/6	5/6
Interval between operations	9 mos.	4 mos.	10 mos.	6 wks.	5 mos	9 yrs.	4 yrs.	3 yrs.	3 yrs.	7 mos.	23 mos.
Symptoms same as before	Yes	Yes	Yes	Yes	Yes	Yes	Yes	—	—	Yes	Yes
Symptoms in contralateral arm	—	—	—	—	—	—	—	Yes	Yes	—	—
Free fragments 1st operation	—	Yes	—	—	—	—	—	Yes	—	—	—
Free fragments 2nd operation	—	Yes	—	—	—	—	—	Yes	—	—	—
Fusion level	5/6/7	6/7	5/6	4/5/6/7	5/6/7	6/7	4/5/6/7	6/7	4/5/6	5/6/7	5/6/7
	← Complete relief →							Partial relief	← Complete relief →		

*Severe multiple level spondylosis.

†Intrinsic atrophy remains, occasional neck pain.

‡Operated 2X posterior within 10 days.

Removal of the posterior longitudinal ligament may produce severe neck pain, usually at the base, and radiation into the shoulders. This pain may last three to five days, but it has disappeared by the seventh day in all patients. Blood dissecting along the epidural space may be the cause.

Bone Graft Fusion

It is possible to remove a graft at a later date and replace it with a subsequent solid fusion. Patient No. 57 had a three-level fusion, and his persistent postoperative arm pain led the surgeon to believe that the C6/7 space had not been cleaned out adequately and the roots decompressed. Two weeks after the first operation the C6/7 plug was removed and the space curetted thoroughly. The graft was replaced and the patient was relieved of pain.

Selective myelography has been done several months after surgery in a few patients. The defects seen originally have been absent. In time fusion per se will not melt away lateral foraminal spurs.

Results

The initial chief complaint of each patient in the group was noted. Nine percent complained of arm paresthesias, six percent noted weakness as the first problem, and 85 percent had pain in the shoulder and/or arm. Many had a combination of complaints, but only the chief complaint was listed for this part of the study.

Follow-up periods ranged from five months to six years. Patients seen at intervals of less than five months were not included except in the "immediate relief" group. Fifteen patients had paresthesia as the most significant complaint; eleven noted immediate relief the day after surgery. Seven patients were followed for longer than five months; five of these had excellent results: they were symptom-free. Two patients were judged fair; they still had residual symptoms.

Ten patients complained initially of weakness. Only two were seen for five months or longer; one had an excellent return of muscle strength and the other, a fair return.

Of 133 patients who presented with shoulder and/or arm pain, 121 (90 percent) obtained immediate relief by the first or second postoperative day.

Sixty-seven patients were followed for longer than five months. Thirty-nine patients had excellent results: they were asymptomatic; 21 had mild to minimal symptoms and were considered to have a fair result; and the condition of the other seven was unchanged and, therefore, poor.

Trauma

The 32 patients treated for trauma consisted of 29 males and three females (Figure 8); 73 percent of their injuries occurred when they were less than 30 years of age. Twenty-five patients were injured in automobile accidents, four while diving and three by falls.

Although it is impossible to differentiate fracture types, bony injuries have been assigned to three broad categories. There were eight subluxations, eight fracture-dislocations, and 16 comminuted-compression fractures.

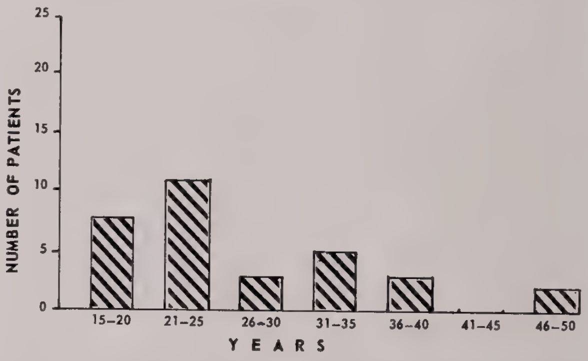

Fig. 8—Distribution by age of patients with trauma.

Absence of Neurologic Correlation

The degree of neurologic injury has no correlation with bony injury (Table 3). For purposes of simplicity the "upper-lower extremity" includes quadriplegia and quadriparesis, "upper extremity" is reserved for patients with arm involvement only, and the last category is "no deficit." Six of the nine patients in the last group complained of significant pain; three had radiating arm pain, and three had persistent neck pain prior to fusion. This small sample represents a most fortunate group of patients. Only two of the eight major injuries were complete; five patients became ambulatory, and one patient, a female, developed quadriparesis after two posterior fusions had failed. A complete 90-degree angulation of C5 on C6 developed. Reconstruction of the neck was done after a posterior laminectomy, and the cord was found to be a ribbon. With traction applied, an anterior approach was done three weeks after the laminectomy. Half of the C4 body and all of the C5 and C6 were removed, and a strut graft was inserted. One and one-half years later the patient had no neck or arm pain. She had complete bowel and bladder function, she could feed herself, and she could ambulate a few steps with assistance. A Brown-Sequard sensory pattern remained with atrophy of intrinsics and a basic quadriparesis. It should be emphasized that not a single one of the five patients was considered to have become ambulatory as a result of the anterior cervical fusion. All of them had either a temporary quadriplegia that had improved markedly before operation, or a quadriparesis that did not preclude ambulation.

Frontal Exploration and Fusion

The author believes that all bony injuries of the neck require frontal exploration and subsequent fusion regardless of the severity or the type of neurologic injury. Patients with complete or partially complete cord injuries benefit from surgery which allows early rehabilitation. This is the single most important factor in the management of these patients. Prolonged traction does not guarantee bony fusion. An eggshell callus was noted in one patient four months after injury; his C6 body had also slipped forward and become badly angulated, with the result that he was quite unstable.

Often realignment is possible in patients who have angulation associated with subluxation. Skeletal traction is applied before fusion, but realignment is not always successful. Patient No. 1 was angulated and subluxed (C6 on C7), but seven months later he was unchanged. Experience of this type has led to body removal and insertion of "bread loaf" grafts. These are pieces of iliac crest with cortical bone on three sides cut to size.

The patient who presents with an anterior tear-drop fracture associated with a compression fracture and posterior displacement, a subluxation or a posterior tear-drop fracture, will certainly produce a hard ridge as the years go by. Prophylactic fusion may preclude a transverse myelopathy if no deficit has occurred with the initial injury.

A posterior decompressive laminectomy may not provide relief from root pain. Patient No. 22, a 22-year-old female, gained relief from left arm pain only after an anterior fusion. Her decompressive laminectomy did not help. She had a compression fracture of C6 with an anterior tear drop.

Skeletal traction and cast immobilization for the usual three-to-four-month period does not guarantee stability. After Patient No. 23, a 34-year-old male with a compression fracture of C5, had been in skeletal traction for six weeks, he was placed in a Minerva jacket for three months. One year later his neurological deficit had increased and he was noted to be subluxed; a myelogram confirmed the C5/6 defect. Realignment was gained with a fusion.

Patient No. 28, a 28-year-old male, presented with a lower extremity paraparesis and weak hand intrinsics. The C7 comminuted fracture was unstable, and at operation the posterior longitudinal ligament was noted to be ruptured. A large free central fragment was lying adjacent to the dura.

Posterior tear-drop fractures are potentially serious hazards. Patient No. 40, with a comminuted C5 body, had a free piece of bone extending 13 mm back into the canal. The resistance of the spinal cord to such abuse is

TABLE 3
Degree of Neurologic Injury

	No. of Patients
Upper and Lower Extremity	8
Subluxation	3
Fracture-dislocation	1
Comminution-compression	4
Upper Extremity	13
Subluxation	4
Fracture-dislocation	4
Comminution-compression	5
No Deficit	9
Subluxation	1
Fracture-dislocation	1
Comminution-compression	7
Brown-Sequard Syndrome	2
Subluxation	1
Comminution-compression	1

amazing at times; the patient had no neurologic deficit.

The best method of management for fracture dislocations is: (1) initial skeletal traction, (2) myelography, (3) anterior fusion, (4) maintenance of skeletal traction for four weeks, and finally, (5) immobilization in plaster or in a rigid cervical collar for three months.

The anterior approach is ideal for the patient with an acute central cord injury. Patients treated during the later period not covered in this report were found to have large central free disc fragments, and they presented the characteristic syndrome of weak arms and good legs. Cervical bodies that are badly smashed and malaligned can be removed. Actual reconstruction of the neck can be done with strut grafts (Table 4, Figures 9 through 13).

Long Tract Myelopathy

Patients with long tract signs regardless of symptomatology and with x-ray evidence of osteoarthritic cervical spurring are discussed in the myelopathy category. Twenty-three pa-

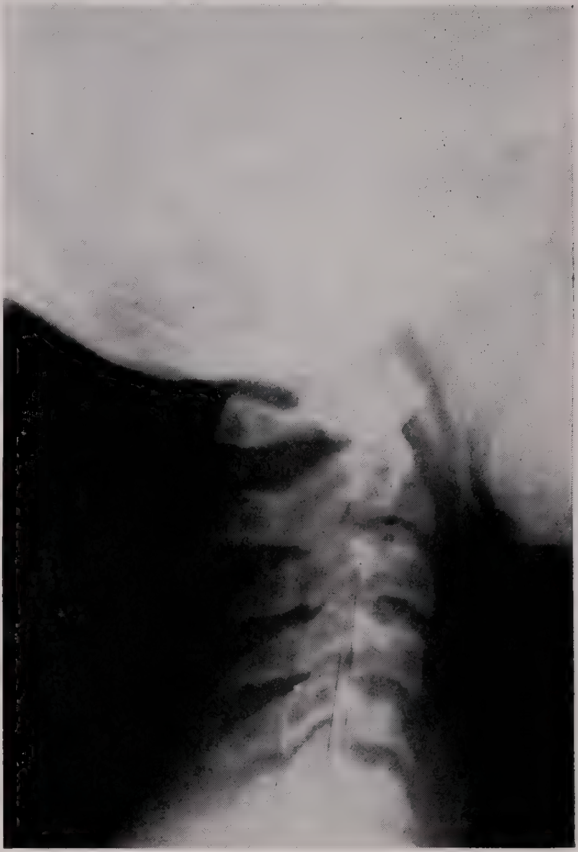

Fig. 9—Fracture-dislocation, no deficit.

TABLE 4
Composite of Trauma Cases

Case Number	Subluxation Only	Fracture-Dislocation	Angulation	Comminution	Anterior Tear Drop	Posterior Tear Drop	Subluxation	Upper & Lower Extremity	Upper Extremity	No Deficit	Brown-Sequard	Myelogram
1		6/7	X				X			Pain arms		Not done
13				5	X					Pain arms		Not done
20	6/7							X				Not done
22												Normal
23				5							X	5/6 Defect
28				7					X			Not done
33				7						Pain arms		6/7 Defect
40				5		X			X			Not done
43		4/5							X			Normal
44	4/5								X			Not done
62				5						X		Not done
52		5/6						X				Not done
64				6	X					X		6/7 Defect
78	3/4										X	Not done
91		4/5								Neck pain		Not done
102		3/4							X			Not done
109	3/4								X			3/4 Defect
116				6						Neck pain		Normal
130				7				X				Not done
150	6/7								X			Normal
151				6				X				6/7 Defect
154		5/6								X		5/6 Defect
164	3/4							X				3/4 Defect
166		2/3								X		Not done
172	4/5								X			4/5 Defect

tients, consisting of 22 males and one female, were seen with long tract signs. Their age range was from 22 to 57 years; the average age was 40 years.

Trauma that occurred considerably earlier or recently was a causative or an incidental factor in four patients. One other patient, a 47-year-old male, had proven hypoxia of traumatic origin. Five years previously he had had an anaphylactic reaction to pentothal and had become apneic. After a tracheostomy he had awakened with a left-sided weakness and hyperreflexia that cleared in 24 hours. There were no cranial signs or symptoms, but five years later he began to have gradually progressive weakness of the arm and leg.

Single Catastrophic Incident

Some patients presented with a single catastrophic symptom, of considerable interest because of its uniqueness. One patient had complete numbness of all extremities for 20 minutes after a skiing fall; one had his legs buckle while dancing; one had from 50 to 100 electric shocks in the arms while playing handball, i.e., a Lhermitte sign; one fell down while running because of leg incoordination; one was unable to run for cover during an air attack because of leg incoordination; one was unable to move his arms or legs for two hours after a fall; one jumped into a swimming pool during survival training (with marked weakness of arms and legs); one was taken off the baseball team because of stumbling too often while running bases; and one noted the ascent of the sensory level from the feet to the nipple line in one week.

Pain

The symptoms in the upper extremities of patients with myelopathy were variable. Half of them had radiating arm pain, neck pain, paresthesias, and weakness as basic complaints. Eighteen had clonus of the lower extremities that was detected at the knee, the ankle or both; nineteen had hyperactive reflexes; fourteen had spastic gaits, and four had a Lhermitte sign. Incoordination of an arm or leg or both legs was a notable complaint in more than one half of the patients.[13] Eleven (almost half) had a sensory level to pin, and ten of these 11

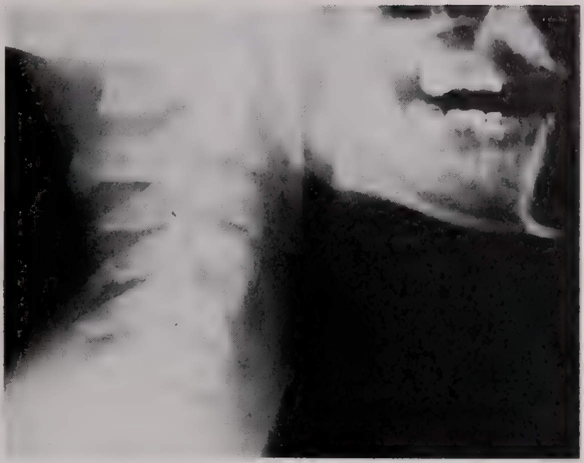

Fig. 10—Fracture-dislocation, two months postoperative.

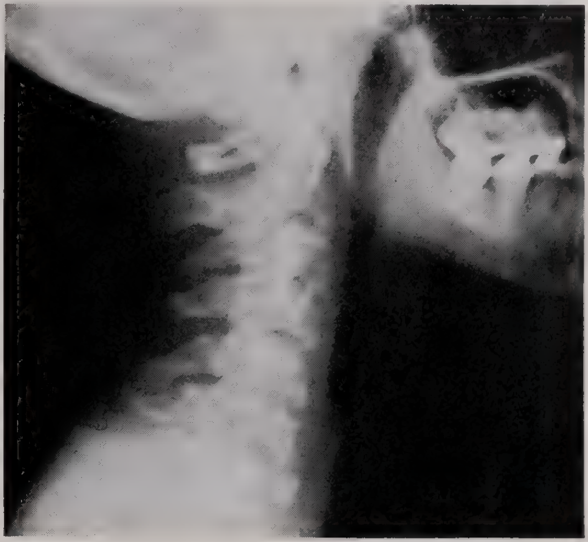

Fig. 11—Comminuted-dislocated fracture.

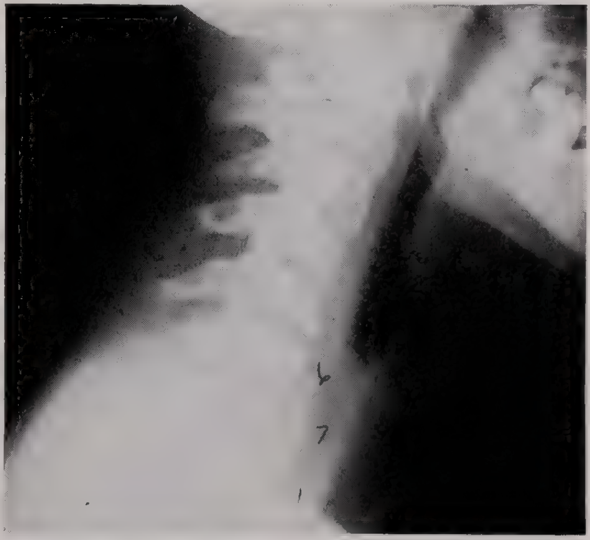

Fig. 12—Comminuted-dislocated fracture two months later.

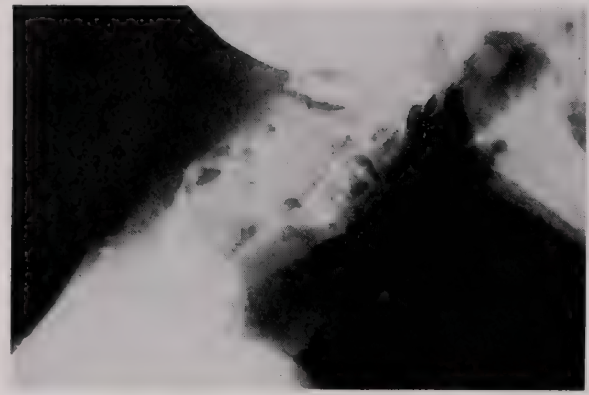

Fig. 13—Strut graft.

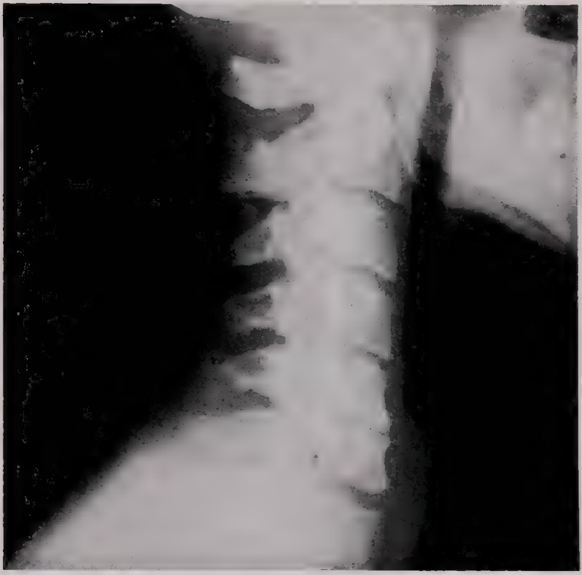

Fig. 14—Spondylosis—long tract signs, preoperative x-ray.

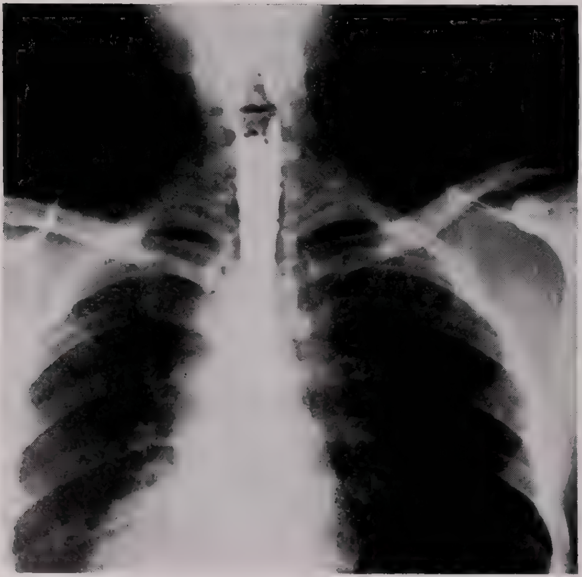

Fig. 15—Spondylosis—long tract signs, myelogram.

were between T4 and T8. It is presumed that a compromised blood supply was the cause. Three patients were classified as Brown-Sequard types.

Radiographic Findings

Radiographs of the neck disclosed hypertrophic spurring, interspace narrowing, and foraminal encroachment in the 23 patients. Myelographic defects of a severe nature were also observed in all patients. A block was found in nine, single-level defects in six, and multiple level defects in the remaining eight. Cerebrospinal fluid protein levels failed to correlate with the severity of disease.

Fusions were done at one level in 11 patients (C3/4 in three, C4/5 in two, and C5/6 in six); at two levels in nine patients (C4/5/6 in four, C5/6/7 in four and C6/7/1 in one patient), and three levels in three patients (C4/5/6/7). The operative findings were of interest. A free central disc fragment was removed from two patients; a calcified central disc indenting the dura was found in two; eleven had a single-level significant ridge, and the remaining eight had multiple ridges.

The degree of long tract involvement is directly related to the result. Admittedly, it is difficult to evaluate results. A patient is better or he is not; but the yardstick of values is variable. A sincere effort was made to note the disappearance of signs, or at least their reduction; some are negligible, but they are present nevertheless.

Hyperactive reflexes diminished in only four of 19 patients. Clonus diminished in five of 18 patients; one patient who had 4+ clonus before surgery had none thereafter. The Babinski sign was reversed in three of four patients. Seven (50 percent of the patients with a spastic gait) had significantly improved ambulation. Pain was alleviated completely in the 11 patients in whom the symptom was disturbing.

Clinical Classification

Patients have been placed arbitrarily into four grades on the basis of the severity of the neurologic deficit:

Grade I. Minimal (3 cases)

Exaggerated reflexes.

Unsustained clonus at knee or ankle.

Grade II. Mild (2 cases)

Signs of Grade I, and weakness of one or both upper extremities.

A sensory deficit, other than of the trunk.

Grade III. Moderate (17 cases)

Signs of Grades I and II, and weakness of one or both lower extremities.

Gait difficulties.

A sensory deficit including the trunk.

Grade IV. Severe (1 case)

Signs of Grades I, II, and III, and inability to ambulate.

For placement in a group, a patient was not required to have all the signs in any group to qualify.

A complete neurological evaluation was done at the end of one month in all but two patients. Twelve were considered improved on the basis of the lessening of reflex hyperactivity, diminution of clonus, increased strength, reversal or lessening of Hoffmann or Babinski signs, lowering of sensory level, or improved gait. One claimed subjective improvement, but no changes in signs were noted. Seven were unchanged and one patient was worse.

Thirteen patients (56 percent) were reexamined from six months to three years after surgery. The one patient who worsened had shown no improvement by the end of two years. Another maintained his subjective improvement. No change occurred in five who originally were unchanged one month after surgery. Seven of the original group (25 percent) were improved; five of these were felt to be significantly improved.

A comparison of these results with those of Stoops and King[1] or those of Clarke and Robinson[2] is not of significant value because of the small number of cases. However, it seems logical to conduct the operative approach from the side where the basic pathology exists if any attempt is to be made at alleviating or at least halting signs and symptoms (Figures 14 through 17).

Complications

The management of the complications of the anterior cervical fusion operation presents a challenge, but experience has demonstrated that they merely delay recovery.

Complications occurred in 74 patients, including ten who had two complications each and one who had three in this series of 213 patients. No deaths occurred immediately. One patient died of pulmonary cancer 18 months after surgery. The complications, which were of 23 types, were grouped into five categories (Table 5).

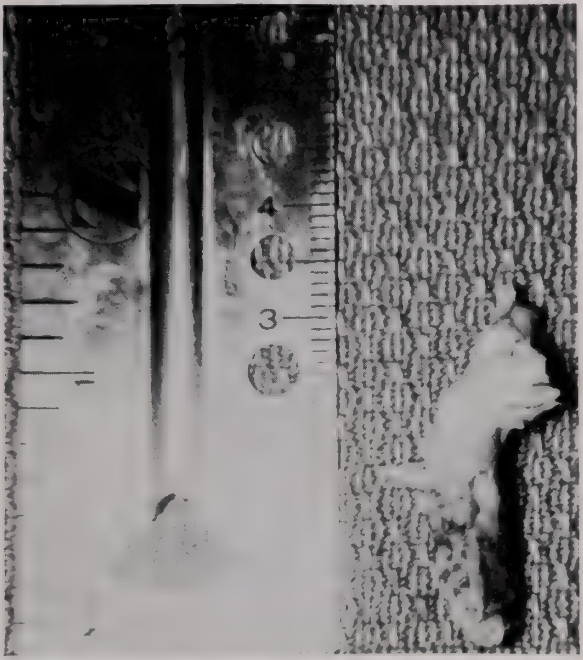

Fig. 16—Large central fragment.

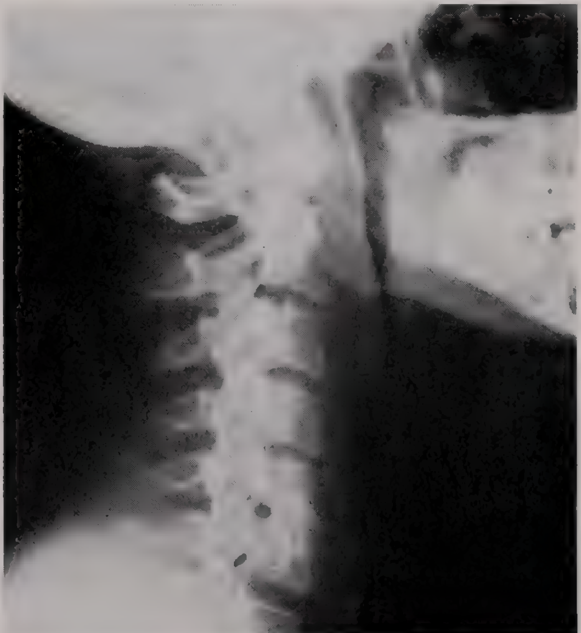

Fig. 17—Spondylosis—long tract signs, postoperative x-ray.

Group I. Complications of Wound Sites

There were 36 complications of wound sites: 12 in the neck and 24 at the donor site. These included 11 patients with superficial infections (eight of the neck and three of the hip); 19 with hematomas (one of the neck and 18 of the graft site); and six with deep wound infections. Three were deep abscesses of the neck with the graft involved, and three were deep infections of the donor site. The latter included two patients with osteomyelitis of the ilium and one patient with a sterile abscess at the donor site six months after surgery as a consequence of a retained sponge.

Superficial wound infections were managed locally, and all healed. Hematoma management varied with the severity, and all cultures were negative. The single hematoma of the neck drained spontaneously on the ninth postoperative day, but healed subsequently. In the hip, a hematoma resolved spontaneously in one patient, required Varidase® in another patient, and cleared with a single needle aspiration in four patients. Multiple aspirations and pressure dressings were required in nine patients, incision and drainage in two, and portable suction as well as multiple aspirations in one patient.

TABLE 5

Complications

	No. of Complications
Group I. Wound Site Complications	36
Neck	12
Hematoma of neck	1
Superficial neck infection	8
Deep neck infection	3
Hip	24
Hematoma of hip	18
Superficial wound infection	3
Deep wound infection	3
Group II. Neurologic Complications	8
Transverse myelopathy	1
Root injury	2
Causalgia, arm	1
"Shawl" hypalgesia	2
Unusual extremity movements	1
Hypalgesia from discogram	1
Group III. Problems with Accessory Structures	23
Recurrent laryngeal nerve damage	7
Horner's syndrome	3
Meralgia paresthetica	6
Dural tears	4
Dysphagia	3
Group IV. Surgical Complications	9
Apnea requiring tracheostomy	1
Infected tong hole	1
Fusion of wrong level	1
Thrombophlebitis of leg	1
Atelectasis	5
Group V. Primary Graft Problems	9
Fusion failure	1
Slipped grafts	3
Graft collapse	5

Deep wound infections posed the most serious problem in Group I, as illustrated by the following cases:

Case Report

Case 1

The first patient, a 45-year-old man, had an uneventful C6/7 fusion for spondylosis. Postoperatively a low-grade temperature elevation persisted for two weeks, but finally resolved by lysis. A non-tender, firm mass was seen in the neck wound two weeks after surgery. X-rays disclosed that a retro-esophageal mass had displaced the tracheal air shadow slightly to the left. Three weeks after surgery spontaneous drainage of seropurulent material occurred, and coagulase-positive Staphylococcus aureus sensitive to penicillin was cultured. At that time the wound was treated locally, and no systemic antibiotics were given. However, x-ray of the neck one month after surgery showed collapse of the C6 vertebral body. Then skeletal traction was applied, and the wound was reopened, irrigated and drained. The graft appeared intact and was not removed. The wound was then drained and closed with wire. After skeletal traction for six weeks, a cervical collar was worn for the next three months. Penicillin and chloramphenicol were administered for two weeks. Three months after surgery, x-rays indicated a solid fusion and good alignment. The patient was asymptomatic when he was seen five months later.

Case 2

The second patient was similar to the first. A two-level fusion was performed at C5/6 and C6/7 for cervical spondylosis. On the ninth postoperative day the patient had a temperature elevation to 102 degrees C and an indurated, warm, erythematous neck wound. After heat was applied, the fever and the neck mass subsided. The patient continued to complain of mild difficulty in swallowing and of neck discomfort. Two months after surgery, cervical spine x-rays showed early destructive changes of the C5, C6, and C7 vertebral bodies with bony sequestra and a retropharyngeal mass (Figure 18). Vinke tong traction was instituted, and exploration of the wound revealed that the C6 body and both grafts were infected. The C5 and C7 bodies were curetted to good bone, and both the C6 body and the grafts were removed. The wound was closed with wire and drained. Coagulase-positive Staphylococcus aureus sensitive to lincomycin grew on culture. Skeletal traction was applied for six weeks, and lincomycin was given. A four-poster collar was substituted for the next four weeks. X-ray five months postoperatively indicated a solid fusion (Figure 19). The patient was asymptomatic at follow-up six months after surgery.

Case 3

The third patient had a C6/7 fusion for cervical spondylosis with no relief of his symptoms. Myelography, repeated two weeks after surgery, disclosed a residual C6/7 defect and a smaller defect at C5/6. Three weeks after the first procedure a second was done at C6/7 and C5/6. Two weeks later spontaneous drainage of purulent material from the neck wound ensued. Coagulase-positive Staphylococcus aureus sensitive to penicillin was recovered. X-rays disclosed osteomyelitis of the inferior body of C5 and of the superior body of C6 as well as resorption of the C5/6 graft.

At re-operation one month after the second procedure the graft was necrotic and the adjacent surfaces of the C5 and C6 vertebral bodies were infected. The C5/6 graft was removed, and the infected bodies were curetted to good bone. The C6/7 graft, which appeared to be solidly fused, was left intact. Cultures taken at surgery yielded coagulase-positive Staphylococcus aureus sensitive to lincomycin and resistant to penicillin. The wound was closed with wire and drained with through-and-through catheters for continuous postsurgical irrigation. The patient was kept in bed for one week before being allowed to be up and about with a plastic cervical collar. Postoperatively, the wound was irrigated with neomycin solution continuously for one week, and the patient was given lincomycin for four weeks. One month after surgery there was x-ray evidence of progressive fusion and he was discharged asymptomatic. No follow-up was available.

Case 4

Osteomyelitis of the ilium occurred at the site of a bone dowel removal in one patient. One week after surgery heat and erythema of the wound were treated with moist heat applications, after which the wound drained spontaneously. Pseudomonas species and beta hemolytic Streptococcus grew on culture. He was treated with chloramphenicol for three weeks. At that time x-rays of the hip disclosed osteomyelitis of the ilium and formation of bony sequestra (Figure 20). The wound was opened and a sequestrectomy was done. The wound was then packed open and allowed to heal by secondary intention. Culture at surgery disclosed Pseudomonas species sensitive to colistin, which had been administered for one month postoperatively. The wound healed after six weeks (Figure 21).

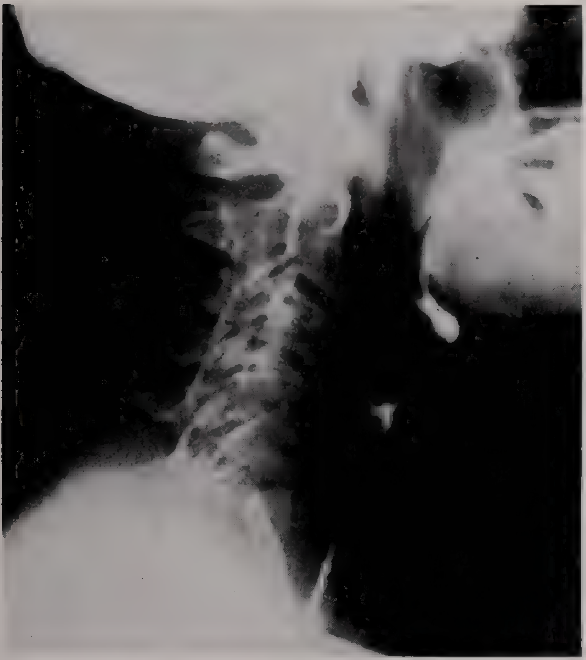

Fig. 18—(Case 2) Before debridement.

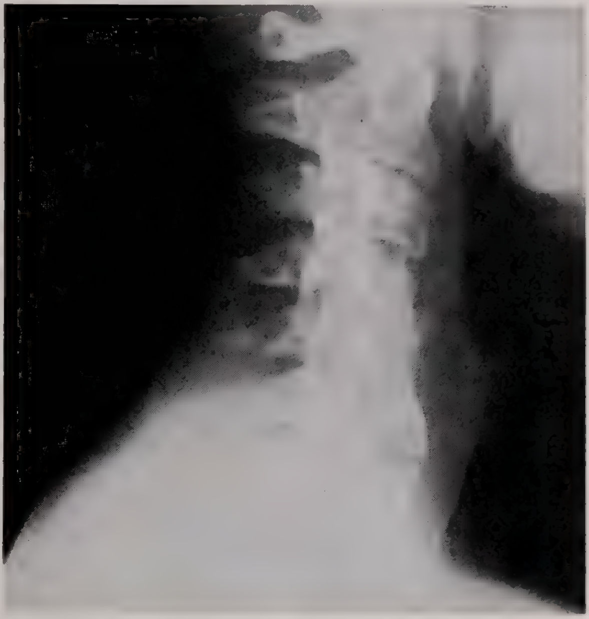

Fig. 19 (Case 2) After debridement.

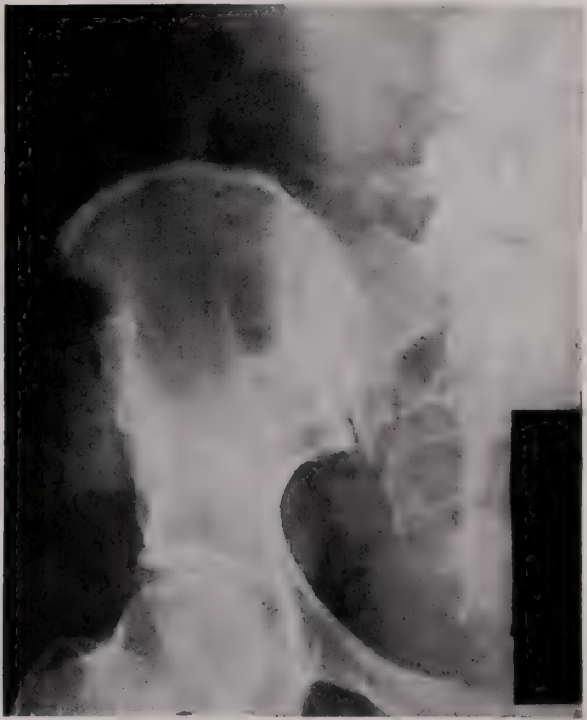

Fig. 20—Osteomyelitis of hip before debridement.

Case 5

One patient returned six months after surgery and complained of a tender mass at the site of the dowel removal. X-rays of the hip showed soft tissue swelling and no evidence of osteomyelitis. When the wound was excised, purulent material escaped; exploration disclosed a sponge. The wound was packed open and allowed to heal by secondary intention.

Group II. Neurologic Complications

Group II consisted of neurologic complications that occurred in eight patients: one had a transverse myelopathy; two had C7 root trauma; two had a peculiar "shawl" hypalgesia; one had causalgia*-like arm pain; unusual flapping extremity movements developed in one patient; and one had left arm paresthesia and upper trunk hypalgesia still present and unchanged eight months after discography. Examples of cases follow.

Case 6

A 47-year-old man had a C5 to C7 block graft for cervical spondylosis. On the second postoperative day he complained of radicular pain and progressive left upper extremity weakness. Lateral cervical spine x-ray disclosed that the graft had been displaced anteriorly, with resultant angulation at C5/6. The patient was returned to the operating room, where the graft was removed, repositioned and reimpacted. A Minerva jacket was applied. On the first postoperative day follow-up cervical spine x-ray again showed anterior displacement of the graft. Skeletal traction was instituted with a 10-pound weight, but progressive displacement of the graft persisted.

Again on the seventh postoperative day the patient was taken to the operating room, where the graft was revised and replaced. Skeletal traction was continued, and the patient seemed to do well for seven days postoperatively. Then urinary retention developed. Bethanecol, 10 mg, was given subcutaneously and 15 minutes later the patient was found unresponsive and in shock. After a quick response to resuscitation, he was found to be quadriplegic. Over the next 20 minutes he moved the four extremities progressively, but remained quadriparetic. Sensation was intact and reflexes were equally diminished bilaterally in the upper extremities, but hyperactive in the lower extremities. He had no pathologic reflexes. On lateral x-ray of the cervical spine, the graft appeared to be tilted. The superior end was displaced anteriorly, the inferior end posteriorly, and the graft was impinging on the spinal canal. The graft was quickly removed and the patient maintained in skeletal traction. Quadriparesis improved progressively; skeletal traction was discontinued after eight weeks and the patient was ambulated.

Twelve weeks after the last surgery he was ambulatory and had no evidence of spasticity; however, mild distal paresis of the upper extremities persisted. The reflexes remained hypoactive in the upper extremities and hyperactive in the lower extremities. Bilateral upturned toes were present.

Case 7

Injury to the left C7 nerve root had occurred. Preoperatively he presented with pain and paresthesias in a C7 distribution in the left upper extremity. Examination disclosed moderately weak triceps C6 and C7 hypalgesia, and an absent triceps reflex, all on the left side. Cervical spine x-rays showed minimal anterior lipping at C5/6 and C6/7, and a cervical myelogram disclosed a large irregular lateral defect at C6/7 on the left. At operation, a large disc fragment was found superior to the root, which was tightly compromised at the neuroforamina. The fragment was grasped with a pituitary rongeur, but during removal the dura was torn. Cerebrospinal fluid filled the wound, and brisk bleeding from the epidural venous plexus followed immediately. Repeated applications of Gelfoam(R) controlled bleeding, and the small dural tear was not repaired. A stamp made of Gelfoam(R) was placed over the dural opening.

Postoperatively there was no cerebrospinal fluid leak, and the wounds healed well. However, the patient had a stormy postoperative course with severe bilateral upper extremity radicular pain, subjective bilateral glove anesthesia, and bilateral weak grip. His condition improved gradually during the next two weeks. At follow-up five months later the patient was free of pain but unable to use the left hand. Examination showed marked weakness of the interossei and lumbricales with weak grip and inability to extend, abduct, or adduct the fingers fully. Atrophy of the dorsal interossei was seen. Anesthesia was present in the left C7 root distribution. Reflexes in the upper extremities were markedly hypoactive, but equal bilaterally.

Case 8

One patient with fusions at C3/4, C4/5, C5/6 and C6/7 for severe spondylosis had protracted radicular pain in the left upper extremity that persisted for four months and then gradually subsided. Another cervical myelogram three months after surgery showed no signif-

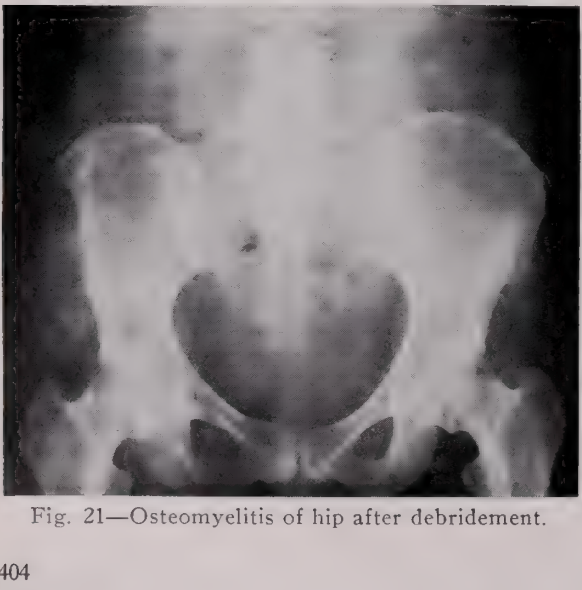

Fig. 21—Osteomyelitis of hip after debridement.

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*See Test Your Word Score Page 457.

icant defect. The pain was managed with analgesics and physical therapy after a two-week trial of steroid therapy failed to alter the symptoms.

Case 9

This patient complained of shawl distribution numbness on the first postoperative day after a C5/6 and C6/7 anterior fusion. Bilateral C4 hypalgesia and hypesthesia were demonstrated, but cleared gradually after persisting for six weeks.

Case 10

The patient complained of pain in the left shoulder and arm. He had decreased pin sensation of the thumb and index finger. The triceps jerk was diminished. Myelography disclosed a left C6/7 defect. Two extruded fragments were removed by the posterior approach on March 19, 1964. He returned three months later complaining of pain in the right shoulder and arm. Cervical spine x-rays were taken again, and a large lateral inferior spur of C6 and spurring at C5/6 were seen. The repeat myelogram disclosed defects at C5/6 and C6/7. An anterior two-level fusion was done on August 9, 1964, and the spurs were removed. Three days after surgery he was noted to have unusual flapping movements of the arms and legs. No hypotension was noted during surgery. Then a jerking movement of the head developed, and a conversion reaction was suspected.

He returned to work and was next seen two years later, when he had only an irregular non-rhythmic tremor of the left thumb and occasional jerking of the left arm and leg. He complained also of numbness of the left side of the body, including the head and face. Reflexes were symmetrical and intact. A recording of the tremor was done using a transducer and an electroencephalograph amplifier. The tremor was irregular in amplitude and frequency. He probably still had some conversion phenomena, although an extrapyramidal cause could not be excluded. He was retired as disabled.

Group III. Problems with Accessory Structures

The complications in Group III involved 23 patients. Seven had recurrent laryngeal nerve damage; three had Horner's syndrome, including one with postoperative apnea requiring tracheostomy; six had injury of the lateral femoral cutaneous nerve; four had dural tears; and three had intermittent dysphagia.

The laryngeal nerve was damaged in seven patients; five of them had a single level C6/7 fusion, one a single level C5/6 fusion, and one a two-level fusion at C5/6/7. All patients had their neck wounds on the right side. Direct laryngoscopy disclosed right vocal paralysis in six patients; the seventh patient did not have laryngoscopy. Two of the seven patients had persistent cord paresis at last follow-up one month and five years, respectively. Of the other five patients one cleared in eight months, one after six months, and two after two or three months, whereas the last patient had persistent hoarseness for ten weeks and then suddenly regained his normal voice, although subsequent laryngoscopy showed persistent mild weakness of the right vocal cord.

Horner's syndrome was present postoperatively on the right in two patients and on the left in one patient. On the right side it was associated with a C6/7 fusion in one patient and with C5/6 and C6/7 fusions in another patient. On the left side the syndrome was associated with C4/5, C5/6 and C6/7 fusions in a third patient (Case 10). At the last follow-up, i.e., eight months, one year, and five years, respectively, after surgery the syndrome was still present.

Case 11

A 52-year-old man presented with a two-month history of pain and paresthesias in the left upper extremity that failed to respond to conservative measures. Examination disclosed left C8 hypalgesia, moderately weak infraspinatus and grip on the left, and absent left triceps reflex. X-rays indicated narrowing and foraminal encroachment by osteophytic spurs bilaterally at C5/6 and C6/7. A preoperative chest x-ray exhibited a slightly widened mediastinum that was interpreted as normal. Myelographic defects were seen at C4/5, C5/6 and C6/7. At surgery, the patient was found to have a soft disc at C6/7 with a free fragment impinging on the left C7 root and hard, degenerative discs at C4/5 and C5/6. Anterior fusion was performed at these levels, using iliac bone dowels. Surgery proceeded uneventfully, and no evidence of excessive trauma was seen at intubation or extubation.

However, eight hours postoperatively the patient complained of a muscle spasm in the left upper extremity that was not relieved by meperidine. An intravenous infusion of 5 per cent dextrose in water (250 cc) with methocarbamol (1 gm) was given over a 30-minute period. Shortly thereafter, the patient suddenly complained of difficulty in breathing, had stridor, and became apneic and cyanotic. Emergency tracheostomy was performed and mouth-to-trachea resuscitation was begun, to which the patient responded immediately and resumed normal respirations. The total time of apnea was estimated to be 90 seconds. A left Horner's syndrome, not present previously, was noted immediately after this episode. The patient recovered quickly and the tracheostomy was removed in four days; he was discharged two weeks after surgery. Shortly after discharge he began to complain of burning pain in the left upper extremity; and when he was seen one month later, he had a pronounced reflex sympathetic dystrophy on the left. He was followed closely at three-month intervals. The Horner's syndrome persisted, and one year postoperatively the patient had a severe coughing bout, after which paraparesis suddenly developed. On admission, a chest x-ray again disclosed a widened mediastinum; spine x-rays showed a destructive lesion of the T3 pedicle, and myelography revealed a complete block at T2. When decompressive laminectomy of C7, T1, T2 and T3 was performed, extradural metastatic adenocarcinoma consistent with a primary lung focus was found. Postoperatively the patient was given palliative cobalt^{60} therapy. He died 18 months after surgery.

Six patients complained of parethesias to the anterolateral thigh after surgery. At the last follow-up, from one to 12 months postoperatively, the symptoms were still present.

Dural tears occurred during surgery in four patients, including one already discussed. A second occurred in curetting an osteophyte that was embarrassing the left C7 nerve root. The small tear was closed with a single 4-0 black silk suture and the patient recovered uneventfully.

Case 12

A third dural tear occurred in a 35-year-old woman who presented with a marked deformity of the neck that was associated with a 15-year history of slowly progressive paraparesis after a C5/6 fracture-dislocation that was sustained at the time of a sudden hyperextension injury. A posterior fusion that was attempted 15 years prior to admission had failed. After a second posterior fusion three years later, the patient noted the gradual development of a neck deformity that was characterized by an immobile neck and flexion of 90 degrees with an exceedingly tender midline, bony prominence at C4. Examination revealed the deformity and moderate spastic quadriparesis. A sensory level to pinprick was present at T2. All reflexes were hyperactive with unsustained ankle clonus and bilateral upgoing toes. Cervical spine x-rays disclosed that C5 was tilted a full 90 degrees on C6. The neck appeared to be solidly fused posteriorly. Cervical myelograms showed marked anterior encroachment of the dye column at C5/6.

Because of the progressive neurologic defect, it was elected to take down the old fusion and to perform an anterior fusion from C3 to C7 using staged procedures. Skeletal traction was instituted, and the patient had the posterior fusion taken down, followed by formal laminectomies from C1 to T2. Three weeks later, the central bodies of C4, C5, and C6 and the intervening discs were removed through the anterior approach, and a block graft of iliac bone was placed from C3 to C7. At surgery it was noted that the cord was greatly compressed anteriorly and that the dura appeared quite attenuated. Postoperatively, the patient had persistent cerebrospinal fluid leakage from the wound and was returned to surgery three days later. The dural tear was identified and closed by suturing a muscle patch graft; no more leakage occurred. The patient was kept in skeletal traction for ten weeks after surgery; at that time she had x-ray evidence of excellent fusion. Neurologically, she was essentially unchanged from the preoperative status.

Case 13

One patient had prolonged dysphagia for one year after anterior cervical fusion. Esophagoscopy and barium swallow were normal. No specific treatment was given, but the symptoms gradually subsided. The other two patients also had normal barium swallows.

Group IV. Surgical Complications

The complications in Group IV, which were observed in nine patients, were not related specifically to anterior cervical fusion. Five had postoperative episodes of atelectasis, manifested by fever, chest pain and x-ray evidence of lung infiltrate. All responded properly to intermittent positive pressure breathing, but two were given penicillin empirically. Left superficial saphenous thrombophlebitis developed postoperatively in one patient, but it was managed successfully with heat and elevation. A localized osteomyelitis of the skull occurred in another patient who was maintained in skeletal traction. Replacement of the tongs and curettement of the involved area led to complete healing.

Fusion was performed at the wrong level in one patient. The patient who required the tracheostomy has been discussed.

Group V. Primary Graft Problems

Primary problems arising from the graft constituted Group V and affected nine patients. Three patients had mobilization of the graft, five had graft collapse, and one patient had failure to fuse with resultant pseudoarthrosis. The last patient is the only one who had a fibular graft. All other patients in the entire series were grafted with autogenous iliac bone. Case examples follow:

Case 14

The second patient had mobilization of the graft after fusion of C4/5 for subluxation, with resultant instability of that joint. Two days after surgery a cervical spine x-ray disclosed a 6-mm forward displacement of C4 on C5. The patient was placed in a plaster Minerva jacket and the displacement reduced to 3 mm which was considered satisfactory. X-rays indicated a good fusion after he was maintained in the plaster jacket for six weeks. Then he was placed in a plastic cervical collar. No more follow-up information was available.

Case 15

One patient who had an anterior fusion at C7/T1 had a collapse of the graft, with resultant subluxation. This man had had bilateral cervical laminectomies at C5/6 and C7 with foraminotomies at C5/6, C6/7 and C7/T1 for cervical spondylosis. At follow-up three months later he was found to have subluxation of C7 on T1. When cinefluoroscopy disclosed motion, an anterior fusion was performed at that level. The patient did well until two months postoperatively, when radicular pain and paresthesias developed in the C7 distribution. Cervical spine x-rays again showed subluxation of C7 on T1 and collapse of the graft. The patient was returned to surgery; a block graft from the iliac crest was applied from C6 to T1, and C5/6 was fused. Postoperatively he was placed in a Minerva jacket for two months and then in a four-poster cervical brace for six weeks. Three months after surgery the patient had a solid fusion and a good alignment, and was asymptomatic.

Case 16

A 19-year-old man who had sustained a compression fracture of C5 with subluxation of C4 on C5 as a consequence of a tumbling accident was immobilized in skeletal traction for four weeks. He had no neurologic deficit. The subluxation reduced initially, but at four weeks he had minimal slip. An anterior fusion was accomplished at C4/5 and C5/6 using iliac bone dowels. He was kept in skeletal traction for one week after surgery and then placed in a cervical collar. X-rays six weeks after surgery disclosed that C4 was subluxed on C5 with 20 degrees of angulation; the C5 body had collapsed anteriorly. He was again placed in skeletal traction and returned to surgery for removal of the old C4/5 and C5/6 grafts and the C5 body, and a block graft in the iliac crest was applied from C3 to C6. For six weeks after surgery the patient was kept in skeletal traction and then ambulated in a four-poster neck brace for three months. X-rays six weeks after the last surgery indicated solid fusion. On follow-up at one year he had an excellent fusion without angulation and was asymptomatic.

Case 17

The one patient with a graft that failed to fuse had a C6/7 fusion using a fibular graft: the only graft of this type. At surgery, only a pencil-lead thickness of cancellous bone was used as a graft. Postoperatively the patient was asymptomatic, but x-rays four months later disclosed a pseudoarthrosis at the C6/7 interspace. However, the patient received no more treatment because he was thought to have no instability in the neck.

Case 18

One patient had the incorrect level fused. At surgery, the C6/7 interspace was mistakenly identified as C5/6 and fused, but this was not known until follow-up cervical spine x-rays were taken. The patient had no more radicular pain and remained asymptomatic for five years after surgery, when right upper extremity pain developed again. Then a C5/6 fusion was performed.

Summary

There were 85 complications in 74 of the 213 patients, making the complication rate 38 per cent. Wound site complications accounted for 16 per cent, neurologic complications for 4 per cent, accessory structure problems for 10 per cent; general complications for 4 per cent, and graft problems for another 4 per cent.

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2. Clarke, E., and Robinson, P. K.: Cervical Myelopathy: A Complication of Cervical Spondylosis. Brain 79:483, 1956.

"You Are What You Eat"

"After studying the eating habits of the American people for a number of years, I found thirty distinct Disease Conditions: vitamin deficient, mineral-starved, cooked-food enervated, sun-cheated, clothes-insulated, coffee-soaked, spice-irritated, tobacco-poisoned, constipation-befouled, oxygen-deprived, sugar-acidified, meat-polluted, starch-clogged, salt-ified, mustard-plastered, pepperized, jelly-bowled, pop-bloated, vinegar-jagged, chocolate-coated, mashed and creamed, toasted and roasted, ice-cubed, tea-tannined, sauce-jaded, night-hawks, morning-deadheads, heat-treated, sex-depleted, and gravy-saturated. That's the average human being today."

—Adolphus Hohensee, Lecture in Denver, 1952*

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*James Harvey Young: The Medical Messiahs: A Social History of Health Quackery in Twentieth-Century America, 1967.

Selfishness is the only real atheism; aspiration, unselfishness, the only real religion.—Zangwill

Nobel Prize Winners In Medicine and Physiology

Charles Nicolle 1928

For His Work on Typhus

"The center of my observations was the native hospital of Tunis. When I visited this hospital I often stepped over the bodies of typhus patients who had come to be admitted and had fallen down from exhaustion at the door. Now there was a singular event taking place in this hospital, the significance of which no one had understood, and which impressed me. The typhus patients were lodged at this time in the common medical wards. As far as the doors of these rooms they scattered the contagion. Typhus developed on contact with them in the families where they were received, and the doctors required to visit them became infected on contact. Moreover the contagion struck the personnel of the admitting offices of the hospital, the employees whose duty it was to collect the clothes and linen, and the laundresses who washed them. And for all this, a typhus patient once admitted to the common ward did not contaminate a single one of his ward neighbors, not an attendant, not a doctor.

"This observation was my guide. I asked myself what happened between the hospital door and the sickroom. What happened was this: the typhus patient was relieved of his clothes and linen, and was shaved and washed. The agent of the contagion was therefore something attached to his skin, to his linen, and something of which soap and water rid him. This could only be the louse."

Nicolle convicted the louse; Paul Miller, of DDT fame, discovered the means to kill it.*

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*Theodore L. Sourkes: Nobel Prize Winners in Medicine and Physiology, 1966.

The Midwife

The midwife occupied a position of great importance in the Colonial community; in fact, she was a community institution. New Amsterdam gave its first midwife, Lysbert Dircken, a house built at public expense, and one of her successors, Hellezond Jaris, was paid a yearly salary of 100 guilders.

Some of the midwives made for themselves records of which they might justly be proud. On her tombstone in the Phillip Street burying ground at Charleston, you find it recorded of Mrs. Elizabeth Phillips (and we have no way of disputing the good lady's mortuary boast) that she assisted at the delivery of some 3000 children. Mrs. Lydia Robinson, of New London, Connecticut, claimed to have helped deliver 1200 in thirty-five years of practice—and never lost a case!

The transition from midwife to male physician was gradual. Dr. James Floyd of Boston returned from London in 1752 equipped to handle obstetrics, and had the temerity to offer himself as a "man midwife." Further South, Drs. Atwood and Tennent, in New York, Dr. Shippen in Philadelphia, and Dr. Moultrie of Charleston, all began the same practice. Many, however, deemed the employment of a male accoucheur scandalous, and for years the old Granny midwife—whose fees ranged from $3 to $8—was still the favourite. The change came about, it is said, because on the Continent fashionable women began to employ men doctors for such cases, and American women of those times (as now) followed whatever Continental styles dictated.*

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*Richardson Wright: Hawkers and Walkers in Early America, 1927.

Artery Shunt for Cyanotic Heart Disease

Intrapericardial Ascending Aorta-Right Pulmonary Artery Anastomosis

BYRON N. DOOLEY, Lt. Colonel, USAF MC
RAYMOND G. ARMSTRONG, Lt. Colonel, USAF, MC
WILLIAM STANFORD, Lt. Colonel, USAF, MC

SINCE THE INTRODUCTION of palliative subclavian pulmonary artery anastomosis in the early 1940s by Blalock and Taussig,[1] thousands of children with cyanotic heart disease have been effectively palliated by these procedures. However, during the intervening years, with the development of cardiopulmonary bypass and surgical techniques for correction of cyanotic congenital heart anomalies, the need for palliative operations has lessened. In newborn infants and young children, where the risk of open heart surgery is high, there is still a definite place in the surgeon's armamentarium for shunt procedures. A great variety of systemic pulmonary anastomoses have been employed, and the principal disadvantages have been with their take-down and closure at the time of open heart procedures.

Because of the difficulty involved in repairing Potts' and subclavian-pulmonary artery shunts at the time of open heart surgery, as well as the difficulty of performing such procedures in small infants, we began to use intrapericardial aorticopulmonary artery shunts in 1965 and have been pleased with the results. This report deals with our clinical experience with the intrapericardial ascending aorta-right pulmonary artery anastomosis in 21 cases and our experience with the closure of this shunt in three children who later came to open repair of their congenital anomalies.

Surgical Technique

All patients were operated upon by the technique described by Hallman and Cooley.[2] With the patient in the left semilateral position, a right anterolateral thoracotomy incision was made and the pleural cavity entered through the 4th intercostal space (Figure 1). The pericardium was opened anterior to the right phrenic nerve and traction sutures placed on the pericardial edges to facilitate exposure.

From the Thoracic Surgery Service, Wilford Hall USAF Hospital, Lackland Air Force Base, Texas.

The posterior parietal pericardium overlying the right pulmonary artery was incised and the right pulmonary artery fully mobilized intrapericardially. A double loop ligature was then placed around the distal pulmonary artery just beneath the superior vena cava. Utilizing a partial occlusion clamp, both the right pulmonary artery and the undersurface of the ascending aorta were secured and parallel incisions made in both the ascending aorta and the pulmonary artery (Figure 2). These incisions are made 3 mm in size for infants under one year of age and 4 to 4.5 mm in size for children in older age groups. Utilizing a continuous suture technique, a side-to-side anastomosis between the two incisions was completed and all clamps released. A continuous thrill should be immediately palpable over the anastomosis after release of the clamps, assuring a patent anastomosis. The pericardium was closed loosely to facilitate drainage and the chest closed in a routine manner.

The shunt was closed in three patients subjected to total correction by placing interrupted sutures through a superimposed longitudinal aortotomy after the patient was placed on extracorporeal bypass with the aorta cross-clamped (Figure 3). This exposure has been excellent and no difficulties have been encountered in closing the shunt. After repair of the ascending aorta, total correction of the cardiac anomaly was accomplished in the usual manner.

Clinical Experience

Since November 1964, the cardiac surgical team at Wilford Hall USAF Hospital has operated upon 21 patients with cyanotic heart disease, utilizing an ascending aorta-pulmonary artery shunt. Other procedures utilized during this period include subclavian artery-pulmonary artery shunt and vena cava-pulmonary artery shunt; however, those patients thought to be candidates for future total correction have preferably undergone ascending aorta-pulmonary artery shunts.

Clinical Indications

The ages of the 21 patients undergoing this

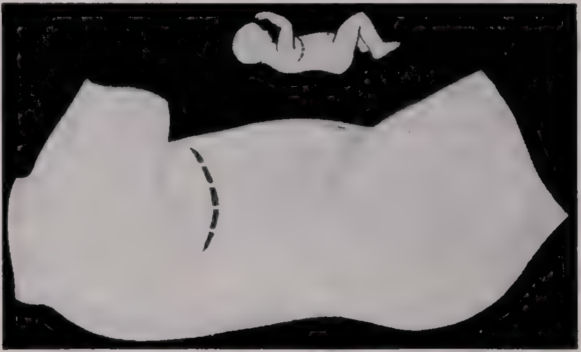

Fig. 1—Standard left lateral thoracotomy position.

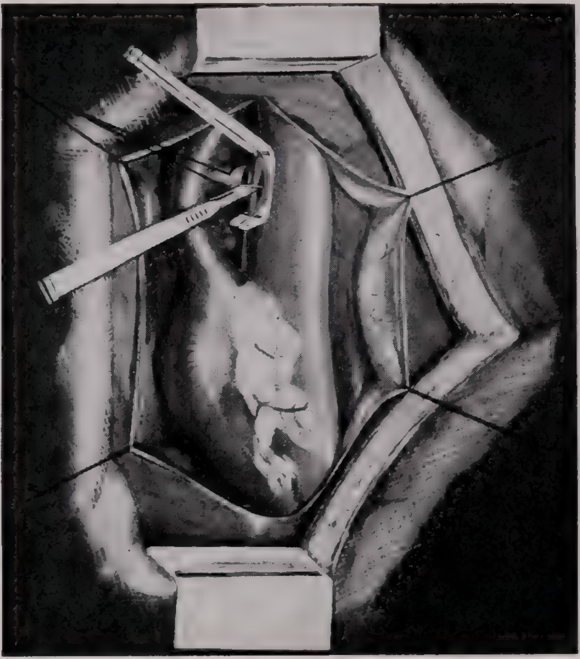

Fig. 2—Parallel incisions for side-to-side ascending aorta-right pulmonary artery shunt.

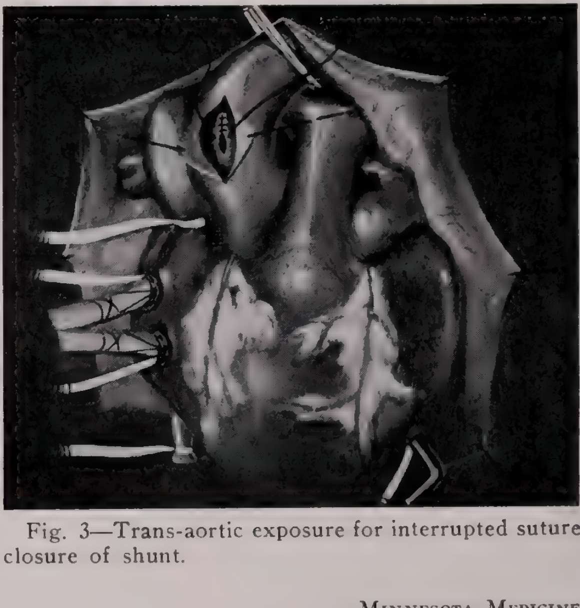

Fig. 3—Trans-aortic exposure for interrupted suture closure of shunt.

type of shunt have varied from six weeks to 21 years, with an average age of less than one year. The operation was performed as a first stage in smaller infants with severe hypoxemia in order to increase oxygenation and survival in infancy prior to total correction at a later date. However, in older patients with uncorrectable lesions, such as pseudotruncus and tricuspid atresia, the shunt was performed because of the small size of the pulmonary artery or anomalies of the aortic arch which did not seem well suited for use of the subclavian artery as a means of creating a systemic shunt. In all patients the main indications for this procedure were severe cyanotic spells, the possibility of strokes, decreased exercise tolerance, fatigue or growth retardation.

Morbidity-Mortality

Among the 21 patients, there were four hospital deaths, giving an overall mortality rate of 19 per cent (Table 1.) Tetralogy of Fallot (16 patients) made up the largest group with two deaths. One patient died of hemorrhage in the postoperative period from a leak at the anastomotic site, the other of a cerebrovascular accident which occurred, possibly, as a result of air embolism or thrombosis during the surgical procedure. Of the four patients with tricuspid atresia, there was one death in the postoperative period due to heart failure from too large a shunt. The other three patients in this group did well.

TABLE I
Hospital Mortality.

Tetralogy of Fallot	16 Pts.	2 Deaths
Tricuspid Atresia	4 Pts.	I Death
Pseudo-Truncus	I Pt.	I Death
19% Mortality	21 Pts.	4 Deaths

All infants with tricuspid atresia operated upon were extremely ill and all were less than three months of age. Although their postoperative courses were much stormier than those of patients with tetralogy of Fallot, all survivors were significantly palliated by the procedure. One 21-year-old patient with a pseudotruncus arteriosus was severely hypoxemic, with extremely small peripheral pulmonary arteries and no main pulmonary artery. A shunt was attempted, but the patient died two days postoperatively of pneumonia and pulmonary insufficiency.

Of the 17 patients who have survived the procedure, all have been effectively palliated and have been followed carefully. Three have come to total correction and closure of the shunt at a later date. In this group, the shunt has very effectively reduced hypoxemia and has successfully afforded a good means of palliation.

We have observed certain complications with this procedure. One patient required reoperation in the postoperative period to narrow the shunt because of heart failure, and another who had thrombosis of the shunt required reoperation one week later. In this case it was technically easy to re-explore the shunt, remove the occluding clot, and re-do the anastomosis.

Discussion

Since 1945 many types of systemic pulmonary artery shunts have been proposed and performed, giving effective palliation to thousands of children with cyanotic heart disease. The original procedure proposed and performed by Blalock in 1945 involved the use of subclavian-pulmonary artery shunt,[1] and that by Potts[3] proposed a shunt between the descending thoracic aorta and the left pulmonary artery. With the advent of extracorporeal circulation for open heart procedures and total repair of tetralogy of Fallot, the situation became somewhat more complicated. The closure and repair of these previously performed shunts is a difficult procedure and is attended with increased morbidity and mortality. Several authors have described various ways of obviating these problems.[4,5] These have included dacron grafts between the ascending aorta and pulmonary artery, as well as the aorticopulmonary artery shunt as originally described by Waterston,[6] which has now become widespread in its use.[7,8,9]

The simplicity and ease of performance of the ascending aorta-pulmonary artery shunt, as well as the fact that it can always be performed through a right thoracotomy incision regardless of the size of the aortic arch, requires little or no mediastinal dissection around the hilum of the right lung and can be closed simply at the time of open heart surgery at a later date, make this type of shunt most appealing.

There are several important factors in the performance of the operation which enhance its successful outcome (Table 2). First is the size of the shunt. Since infants may easily go into heart failure, the shunt should be approximately 3 mm in diameter if the infant is less than one year of age, or 4 mm if older. Older children can tolerate a 4-mm shunt quite nicely without difficulties in most cases. An immediate thrill should be palpable after the performance of the operation; if not, then immediate reoperation should ensue. In our experience, all shunts which have not had immediate thrills or a machine-type murmur over the area have not been open.

TABLE 2

Important Factors for Successful Outcome.

1. Size of Shunt
    - A. 3 mm. Infants under one year.
    - B. 4 mm Children over one year.
2. Immediate Thrill
3. Early Re-operation for Failure
4. Avoid Emboli

Another important consideration is the advisability of early re-operation for cardiac failure, as an infant who develops heart failure after a shunting procedure will not survive. Immediate narrowing of the orifice of the shunt by simple suturing will decrease the size of the shunt and prevent further failure, thus enhancing survival. During the creation of the shunt, air may become trapped in the ascending aorta. Therefore, it is very important to first fill the anastomotic area in retrograde fashion from the pulmonary artery prior to releasing the aortic clamp.

Closure of the shunt in the three patients who have come to open repair has been done through an aortotomy with interrupted suture closure of the shunt from within the aorta. This approach has worked well and we have encountered no difficulties. Closure has been satisfactory and certainly much simpler than taking down a Potts' or Blalock anastomosis. It is possible, however, to cause excessive narrowing of the right pulmonary artery during closure of this anastomosis from within the aorta.[10] Therefore the interrupted sutures should be placed very carefully in order not to produce an acquired pulmonary artery stenosis. We feel that this operation can be easily performed with an acceptably low mortality rate and can provide effective palliation of critically ill, small infants who might otherwise be unable to survive until corrective surgery can be carried out at a later date.

Summary

Twenty-one patients have undergone shunting procedures from the intrapericardial ascending aorta to the right pulmonary artery for severe cyanotic heart disease. Most of these patients have been hypoxemic infants who have had shunts performed in preparation for definitive open repair of the underlying cardiac defects along with simultaneous closure of the shunt. This type of shunt has worked well, has been easy to repair at the time of open heart surgery, and is therefore recommended as a standardized preliminary procedure for any patient, especially small infants who would otherwise have a prohibitive risk for early open heart surgery.

Addendum

The ascending aorta—right pulmonary artery shunt has been performed on six additional patients including one with transposition and tricuspid atresia and one with transposition and pulmonic atresia. There were no deaths among these additional patients giving a mortality rate of 15 percent for the 27 patients treated thus far.

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Nationalism is an infantile disease. It is the measles of mankind.—Albert Einstein

Radioisotope Dilution Assay for Vitamin B_{12}

Experiences

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FOUR COMPONENTS are required for an isotope dilution assay system. The first requirement is that the substance being assayed must be available with a radioactive label. Secondly, a binder must be available which is capable of distinguishing the non-radioactive substance from its radioactive counterpart. Thirdly, the affinity of the binder for the substance being assayed should be independent of the concentration of the substance being assayed. Lastly, there is the requirement for a means of separating the bound substance from the unbound (free), such that the dilution of radioactive substance by the unlabeled counterpart may be measured; i.e., the specific activity of the bound substance changes according to its dilution with the non-radioactive material. If these conditions exist, the principle of radioisotope dilution applies and the substance in question may be assayed without the necessity of repeating a standard curve.[1]

In the measurement of vitamin B_{12} by radioisotope dilution, a labeled form of vitamin B_{12} is available. There are, in addition, two natural binders: Intrinsic Factor, obtained from gastric juice, and normally occurring serum B_{12} binders, Transcobalamine I and II. Both of these binders have been used for the vitamin B_{12} assay.[2,3,4] Intrinsic Factor has been found to adhere to the principle of isotope dilution when using the physiologic amounts of vitamin B_{12} which appear in the serums being assayed.[2] However, Intrinsic Factor has been found to be unstable upon thawing and refreezing and its binding capacity may change in the presence of the serum extract which is to be analyzed.[2,4,6] The transcobalamines have been used, both from normal serum[3] and from patients with chronic myelocytic leukemia who have a high Transcobalamine I and Trancobalamine II ratio.[4] We have used sera from chronic myelocytic leukemia patients with high Transcobalamine I: Transcobalamine II ratios,

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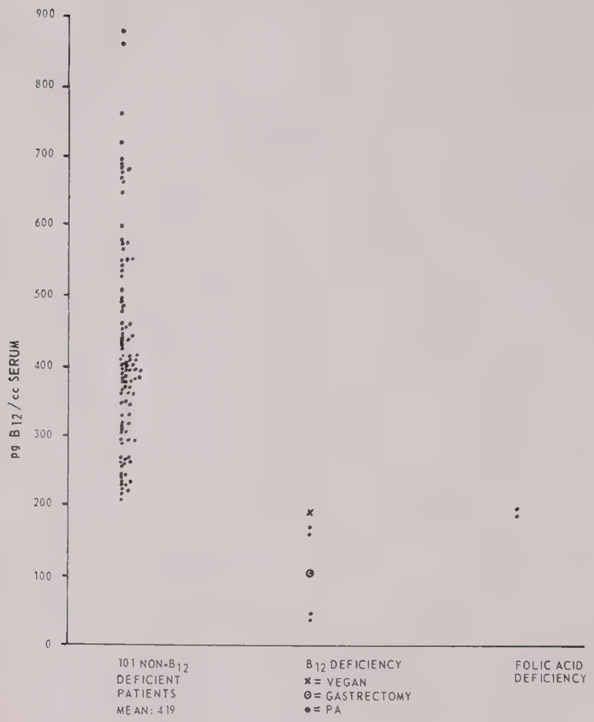

Fig. 1—Plot of 109 serum vitamin B_{12} assays.

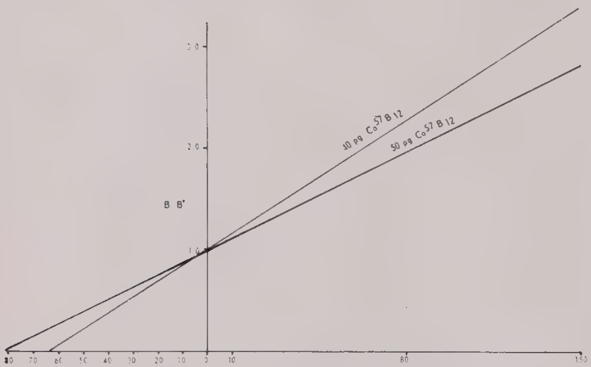

Fig. 2—The principle of isotope dilution is applied where B = C.P.M. bound in the presence of 40 or 50 pg of isotope and B′ = C.P.M. bound following dilution by the addition of 0-150 pg of the unlabeled B_{12}. Extrapolation of lines A & B are found to overestimate the actual amount of isotope by a factor of 1.6.

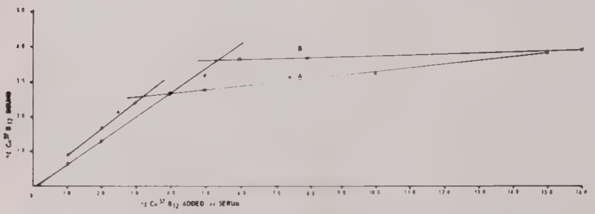

Fig. 3—A plot of the amount of B_{12} bound/cc of serum as a function of the amount of B_{12} added. Line A represents a serum with a Transcobalamine I: Transcobalamine II ratio of 44.3:55.7; line B, 73.6:26.4.

as described by Rothenberg,[4] to determine if this method in our laboratory will: (1) distinguish between normal and low serum vitamin B_{12}, (2) adhere to the principle of isotope dilution, and (3) require a standard curve with each batch assay.

Methods and Materials

$Co^{57}B_{12}$ with a specific activity ranging from 12 c/ gm to 100 c/ gm was used as the isotopically labeled vitamin. Radioactivity was determined with a Picker Nuclear Autowell #2 scintillation counter.

The serum used for the binder was obtained from patients with chronic myelocytic leukemia whose Transcobalamine I: Transcobalamine II ratio was greater than 70:30 as determined by using either the "Baby Column Technique" or starch gel electrophoresis.[7,4]

The assay procedure for vitamin B_{12} was that of Rothenberg[4] who uses two 15-minute boiling periods to extract vitamin B_{12} from its serum binders. One with equal volumes of buffered sodium acetate .68M, PH 4.3, and NaCN, 10 mg/1, followed by an equal volume of .3N NaOH. A dilution of the binder with saline was used such that 70-80% of 40-60 picograms (pg) of isotope was bound. The addition of $ZnSO_4$ followed by $Ba(OH)_2$ is used to precipitate the binders, thus separating the bound from the free vitamin.[4] If Ba $(OH)_2$ is added prior to $ZnSO_4$ it will dissociate the B_{12} protein complex.

The non-labeled vitamin B_{12} used in the standard curve for dilution of the isotope may be stored in concentrations of 1000 pg/cc at 5° C for at least three months, as dilutions of this in our laboratory have given a consistent standard curve from batch to batch (Figure 4).

The unsaturated vitamin B_{12} binding capacity curves were determined by the addition of increasing amounts of radioactive vitamin B_{12} to 0.5 cc serum, followed by a 30-minute incubation at 37°C. The free vitamin B_{12} was then removed by hemoglobin-coated charcoal dialysis according to Gottlieb et al.[8]

Results

The results from 109 serums analyzed for vitamin B_{12} are seen in Figure 1. Of these, 101 have values greater than 200 pg/cc, the mean of these is 419 pg. There were eight sera that had values below 200 pg.

Using the principle of isotope dilution and plotting ratios of B/B′ (Figure 2) against unlabeled vitamin B_{12} shows that the principle of isotope dilution is not obeyed, as the amount of isotope is overestimated by a factor of 1.6.

Figure 3 shows the unsaturated binding capacity curves done with two sera from patients with chronic myelocytic leukemia. One has a Transcobalamine I: Transcobalamine II ratio of 73.6:26.4 and the other 44.3:55.7. The one with the high Transcobalamine I: Transcobalamine II ratio showed little change in its binding capacity once saturation was reached.

Figure 4 represents the mean of three standard curves done in duplicate. The regression line was plotted considering the mean of the duplicate determinations at each level of isotope dilution by 10, 40, 80, and 150 pg of unlabeled vitamin B_{12} for each curve. The binder used in this case was from a patient with chronic myelocytic leukemia whose Transcobalamine I: Transcobalamine II ratio was 72.6:26.4. The greatest variation of any point from the mean of the three standard curves shown as the regression line is 7 pg at levels of dilution from 0 to 80 pg. This value is multiplied by a factor of four when converted to pg of vitamin B_{12} per cc serum because of dilution of the serum during extraction. Therefore, if a mean standard curve is used, the greatest variation to expect would be 28 pg per cc in the range of 0-320 pg per cc. In order to test the precision of the method, four assays were done over a several-month period of time on the same sample of serum obtained from one patient with PA and another with chronic myelocytic leukemia. The mean of the four determinations was 56.5 ± 4.9 (S.E.) pg/ml for the PA patient and 1988.0 ± 28.8 (S.E.) pg/ml for the chronic myelocytic leukemia patient. The chronic myelocytic leukemia serum was diluted so as to fall within the standard curve.

Discussion

Analysis of eight sera gave vitamin B_{12} levels of below 200 pg. Four of these patients had pernicious anemia, one patient was a vegetarian, and another had B_{12} lack, secondary to gastrectomy. There were two patients with folic acid deficiency. There are previous reports of low serum vitamin B_{12} levels in patients with folic acid deficiency.[9] Two of our patients, as indicated in Figure 1, with pernicious anemia had serum values which were in the same range as the values

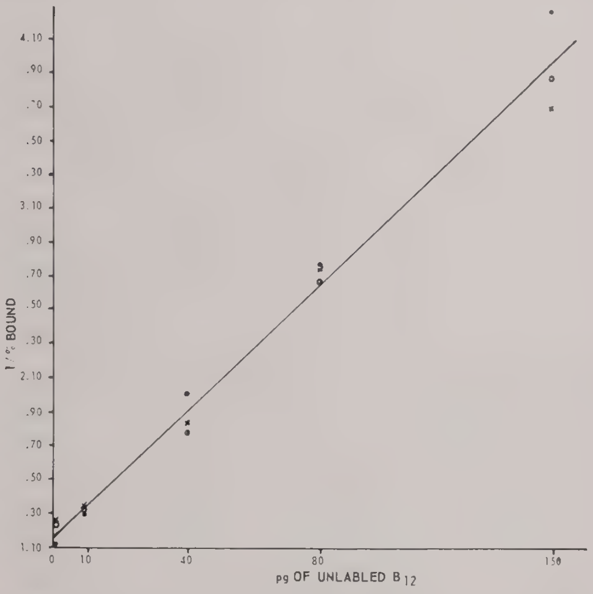

Fig. 4—A mean of three standard curves done over a three-month period of time. Each point represents the mean of duplicate determinations for each of the three curves. The regression line was plotted by the method of least squares.

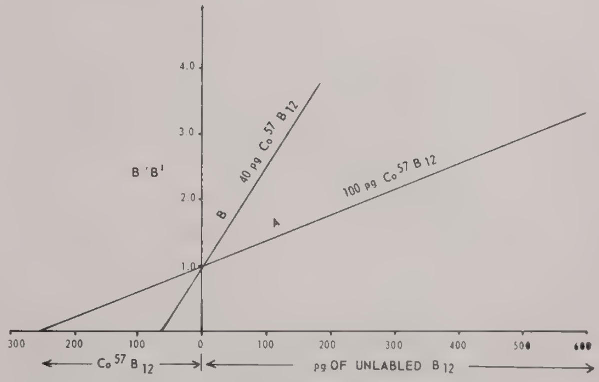

Fig. 5—A plot of B/B′ as a function of isotope dilution by non-labeled B_{12}, where line A represents pooled normal serum used as a binder and B is a serum with a high Transcobalamine I:Transcobalamine II ratio. 100 pg of isotope were used with the normal pooled serum and 40 pg with the high Transcobalamine I serum. Extrapolation reveals a greater over-estimate of the isotope with the normal serum binder.

seen in the two patients with folic acid deficiency. It would appear that a random serum level of vitamin B_{12} could be misleading unless one further investigates the etiology of the "vitamin B_{12} deficiency" as determined by serum levels. However, values below 200 pg/cc should be considered as being low and indicate either B_{12} or folic acid deficiency or both.

Serum containing a high ratio of unsaturated Transcobalamine I: Transcobalamine II as a binder does not obey the principle of isotope dilution as indicated by the overestimation of the isotope by a factor of 1.6 when plotted as B/B′ as a function of unlabeled vitamin B_{12} (Figure 2). This plot allows one, by extrapolation of the curve, to measure the concentration of the labeled vitamin, if the specific activity of the labeled substance is reduced in direct ratio to the total amount of material present with addition of unlabeled substance, i.e., if the principle of isotope dilution is obeyed. There is apparently closer adherence to this principle than is obtained with the use of normal serum as the binder, which has an average Transcobalamine I: Transcobalamine II ratio of 18.8:81.2.[7] Frenkel,[3] using such normal pooled sera as the binder, found that the amount of isotope was overestimated by a factor of 2.5. Figure 5 shows the comparison of Frenkel's data with normal serum as a binder and our data using a binder with a Transcobalamine I: Transcobalamine II ratio of 73.6:26.4 from a patient with chronic myelocytic leukemia. The 100 pg is estimated to be 260 pg by normal serum, while 40 pg is estimated to be 65 pg by chronic myelocytic leukemia serum. This suggests that increasing the concentration of Transcobalamine I as the binder results in closer adherence to isotope dilution kinetics.

Figure 3 shows two binding curves for chronic myelocytic leukemia sera with differing ratios of Transcobalamine I: Transcobalamine II. It should be noted that in the sample with higher Transcobalamine I there is relatively little additional binding with large increases of vitamin B_{12} after saturation is reached. Such is not the case when Transcobalamine I and Transcobalamine II are present in roughly equal amounts. Rothenberg similarly showed a larger increase in the binding capacity of normal serum than Transcobalamine I serum with the addition of increasing amounts of vitamin B_{12}.[4] This may account for the closer adherence to isotope dilution kinetics when using sera with high Transcobalamine I: Transcobalamine II ratio. One could predict that the best binder for the analysis would be the serum fraction containing Transcobalamine I alone.

Because of the lack of adherence to radioisotope dilution kinetics, it is necessary to refer to a standard curve. Our experience with standard curves, using the same binder with a high Transcobalamine I: Transcobalamine II ratio at intervals separated by several months, indicates very close reproducibility (Figure 4). We would support Rothenberg's proposal for using a zero dilution of the isotope with each batch as a check to insure that not only the binder but the isotope remain in the same proportions from batch to batch.[4] Serum values may be determined from the mean standard curve or, as suggested by Rothenberg, they may be calculated from the formula for the straight line where the slope and intercept are known. Using our standard curve, the formula would be pg B_{12} per ml serum = [54 (1/FB)—94] x dilution.

Summary

Serum with high unsaturated Transcobalamine I: Transcobalamine II ratios from patients with chronic myelocytic leukemia has been used, as described by Rothenberg, as the binder for a radioactive dilution assay of serum vitamin B_{12}. With this binder, values of below 200 pg should be considered abnormal and may represent vitamin B_{12} and/or folic acid deficiencies. The assay does not adhere to the principle of isotope dilution kinetics and thus requires a standard curve. Due to the stability of the binder, the standard curve is reproducible from month to month and thus does not require repeating with each batch assay.

References may be secured from the author or the reprints.

Every great advance in science has issued from a new audacity of imagination.
—John Dewey

Subtalar Inflammatory Response to Stress

A Cause of Foot Pain

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PATIENTS WITH PAINFUL FEET present from all walks of life with myriads of symptoms and etiologic factors.[1,2] The knowledge that feet become sore when stressed with unaccustomed walking is a personal observation familiar to all. The label of "tenderfoot" placed on the newly arrived traveler by the western mountaineer is legend. The painful foot of the basic trainee in the Armed Forces sends him to sick call with complaints that vary in number and intensity relevant to the amount of stress from the marching and standing required by the duty schedule.

Symptoms

One group of patients described pain in the foot below the ankle that became worse on standing and marching, but was eased by rest. Acute pain was reproduced when the rotary stress of the subtalar joint caused movement of the os calcis with the ankle stabilized; and frequently there was associated pain over the peroneal or posterior tibial tendons and acute pain on pressure over the sinus tarsi. If the duration was long enough there was spasm and tenosynovitis of these tendons. Most patients gave a history of a sedentary occupation prior to entry into the Air Force.

These observations suggested an acute inflammatory response in the subtalar joint caused by repetitive stress to the subtalar joints as an etiology for foot pain.

Anatomy and Function of the Subtalar Joint

Lapidus[3,4] emphasizes the subtalar joint as having two compartments, the anterior talonavicular and the posterior talocalcaneal, separated by an intra-articular ligament known as the interosseous talocalcaneal ligament. This ligament begins as a portion of the united capsules of the talonavicular and talocalcaneal

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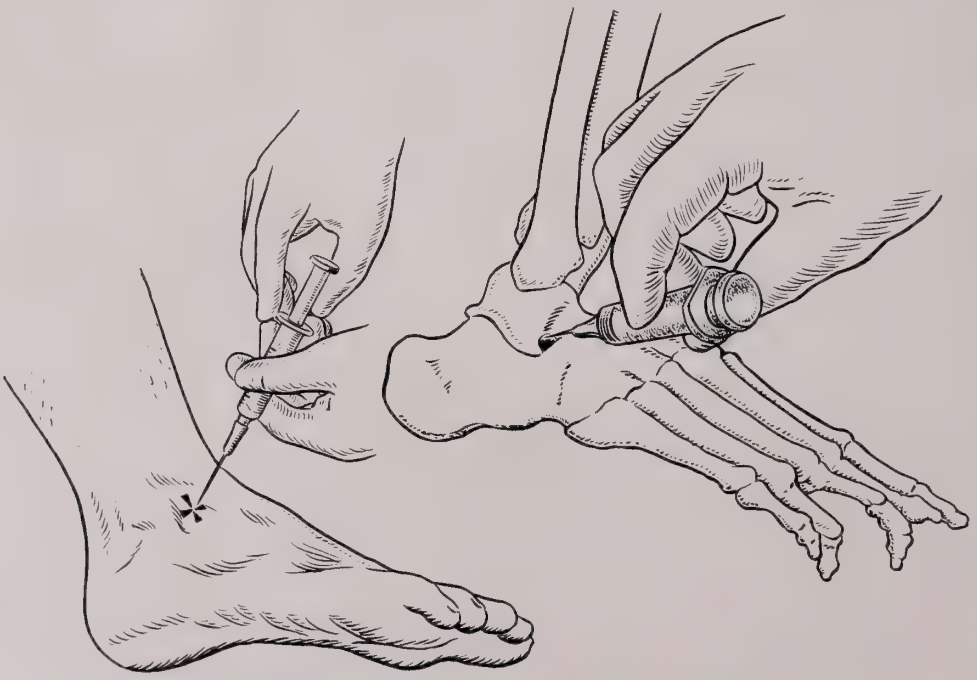
joints in the depths of the sinus tarsi, and passes obliquely from an anterolateral to a posteromedial direction across the subtalar joint attaching to grooves in the talus and calcaneus to form the strongest bond between these bones. The axis of motion of the subtalar joint is not the longitudinal axis of the foot, but runs obliquely from superior-medial-distal to plantar-lateral-posterior.[4-9] This axis crosses the interosseous talocalcaneal ligament and, since subtalar movement is in a compound arc, the ligament must absorb repetitive twisting stress at the extremes of motion, thereby becoming tense on inversion and relaxing on eversion.

Since no muscles insert on the talus, it can only follow passively the movement of associated bones. Because of the oblique subtalar axis of movement, the gastrocnemius-soleus tendon inserting medially on the os calcis probably always acts as an invertor of the foot. With the heel in valgus position during weight-bearing, each push-off places a strong varus pull on the os calcis and produces a rotary subtalar motion. This muscle group also provides the greatest amount of inversion to the foot.[10] Therefore, walking, jogging and running are direct stretches of the interosseous talocalcaneal ligament. The protective device of the foot is the contraction of the peronei, which neutralizes the inversion force.

Material and Methods

With these anatomical concepts in mind, it was thought that some of the painful foot problems seen might be due to acute inflammation of the subtalar joint and the intra-articular talocalcaneal ligament, and that resolution of this inflammatory response would resolve the painful foot. A short trial of injecting the subtalar with varying amounts of local anesthetic and steroids produced encouraging short-term results and a clinical study was entered upon.

Basic airmen who presented to the Orthopaedic Clinic with painful feet, pain on passive subtalar motion, and tenderness over the sinus tarsi were treated. Many of these airmen had tenderness over the peroneal and/or posterior tibial tendons, and limped with the foot everted and peroneal muscles in spasm. X-rays were made on all patients to exclude tarsal coalition anomalies and to rule out recent or remote trauma. All were questioned as to motivation for a career in the Air Force, and those who appeared to be manipulating in order to escape duty or obtain a medical discharge were excluded. Twenty airmen were selected for



Figure—Technique of injection of subtalar joint.

therapy.

Treatment

Treatment consisted of aseptic injection of the subtalar joint with a mixture of 3 cc of 1 per cent lidocaine, 1 cc prednisolene tertiary butyl acetate, and 1 cc dexamethasone. Usually 3 cc of the solution were injected.

The technique of injection was to pass a No. 21 needle across the sinus tarsi into the posterior portion of the subtalar joint (Figure). To enter the joint initially could prove difficult; but it was accomplished by "walking" the needle across the substance of the os calcis until penetration of the joint was felt. After injection the airmen were returned to duty with the advice that they might have some post-injection pain and the request that they remain off their feet as much as possible for the remainder of that day, but resume full duty the next day. Six airmen had both feet injected and 14 had one foot injected.

Results of Treatment

Of the 20 airmen treated, 19 had good results and completed basic training without enough loss of duty time to require that they be set back in their training schedule. One airman did poorly and was treated subsequently with molded arch supports, repeat injections, and prolonged rest, without improvement. He was separated from the Service.

Follow-up was from one to three weeks. The airmen proceeded to their duty assignments and were lost to long-term follow-up.

Discussion and Summary

Many aspects of the painful foot are unsolved. The sinus tarsi syndrome reported by O'Connor,[11] and later by Brown,[12] is one example. The role of the subtalar joint in relation to the peroneal spastic flat foot has been studied[13-15] and seems to be implicated as an etiological factor in the painful foot.

This paper has attempted to introduce a concept of the role of the subtalar joint in the acute painful foot syndrome seen in young adults and precipitated by prolonged foot activity. Basic anatomical considerations have been discussed and a program for symptomatic relief of the painful foot has been based on the concept of an acute inflammation of the subtalar joint, secondary to repetitive stress, as an etiological factor.

Twenty patients with an acutely inflamed subtalar joint and painful foot have been treated by injections of a local anesthesia and steroids to the subtalar joint with good results in nineteen. This experience strongly suggests that an inflammatory process of the subtalar joint and the intra-articular talocalcaneal ligament is the etiology.

The results of the study on a short-term basis have been gratifying, and the authors have been sufficiently encouraged to extend the treatment beyond this limited clinical study.

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It requires a very unusual mind to undertake the analysis of the obvious.—Alfred Whitehead

The Bigger They Come, the Harder They Fall

The ancient version of "the bigger they come, the harder they fall," was written by Herodotus (484-424 B.C.) and is concerned chiefly with obesity. "You may have observed how the thunderbolt of heaven chastises the insolence of the more enormous animals, whilst it passes over without injury the weak and insignificant: before these weapons of the gods you must have seen how the proudest palaces and the loftiest trees fall and perish."

Ptolemy VII was one of the fattest men of antiquity who was so obese that he could not walk unless supported from both sides. Another tiny tot of antiquity was Denys of Heraclea, who was so fat that he hardly dared to go to sleep for fear of suffocation.

Obesity has been found in all parts of the world from the Eskimos and their whale blubber, to the South Africans and their vegetable oils and human steaks. The civilized, the aborigines, no peoples have escaped the glutton with his physical handicaps and retardation. Socrates writes, "Bad men live that they may eat and drink, whereas good men eat and drink that they may live." Saint Jerome (345-420 A.D.) echoes: "A fat paunch never breeds fine thoughts." A young lad of Philadelphia is said to have become so fat that he was unable to get out of his house for at least five years. A man from North Carolina attained a round thousand pounds and a woman from Baltimore is reported as blossoming 850 pounds. Daniel Lambert of Leicester at twenty-three years of age weighed 448 pounds, at 39 years of age he weighed 779 pounds, measured three yards around the body and one yard around the leg.

Probably more jokes are directed at the obese individual than to any other type of human being. Whenever the cartoonist or the joke writer runs out of good material, it is always easy to fall back on the cushion of obesity, for the fat sufferer is the natural butt of the joke-smiths. The movies, the radio, the journalist, everybody takes advantage of Fatso.*

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*Saul, F. William, M.D.: Pink Pills for Pale People, 1949.

Acute Abdominal Syndrome

Goldstone and Le Marquand described a syndrome observed in 13 European servicemen on duty in West Africa that simulated acute abdominal disease. The condition was characterized by fever, right upper abdominal pain, and muscular rigidity. Symptoms appeared gradually, reaching a peak within a few hours. The pain sometimes spread to the entire right side of the abdomen and loin. Considerable rigidity was present with relatively less tenderness in the painful areas. Usually there was diminished movement of the right side of the chest and diaphragm, occasionally accompanied by shoulder pain. The prognosis was good with a rapid, spontaneous improvement in most cases. Goldstone and Le Marquand concluded that these patients most likely had an abortive form of perinephric staphylococcal infection. They also suggested that cases which simulate a perforated peptic ulcer with negative findings at operation may be similar to those described here.

Durham, Robert H.—Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York

Significance of Late-Developing Reactions in Allergy Skin-Testing

Clinical Correlations

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ROBERT E. SMITH, Colonel, USAF, MC*

THE ALLERGY SKIN TEST has been of inestimable value in the identification of specific antigens to which an atopic† person may be sensitive. Many investigators have discussed at length the interpretation of the immediate wheal and flare reaction which occurs within 15 to 30 minutes, and general agreement exists with respect to the positive significance of these reactions.[1-11] However, many physicians who perform these tests occasionally find that several hours may elapse before the skin tests become positive.[3] It has not been common practice to have patients look for, or report, such reactions.

This paper presents an attempt to evaluate the significance of skin tests that were negative at 30 minutes but positive a few hours later. Interest in this investigation was stimulated by the return of a middle-aged woman with classical evidence of allergy by history, physical examination and laboratory data, but entirely nonreactive intradermal skin tests even one hour after testing. When the need for retesting was mentioned, she asked whether it was essential and stated that her arms had been sore, swollen and itching for several days after the first tests.

Material and Methods

All new patients referred to the Wilford Hall USAF Hospital Allergy Clinic must give a complete history and undergo a complete physical examination. Patients who have a probable diagnosis of inhalant allergy and reside in the local area are skin-tested to the 24 antigens most significant for this geographical area.

The Tested Antigens

These antigens are: cottonwood, American elm, white ash, hackberry, oak, pecan, mesquite, mountain cedar, grass mix (Bermuda, Johnson and Timothy), privit, franseria, pigweed, Russian thistle, ragweed mix, scrub elm, house dust, hormodendrum, alternaria, spondylocladium,* helminthosporium, fusarium,* aspergillus* mix, penicillium mix and phoma*. In addition, all patients receive scratch tests to cat dander, dog dander, feathers, kapok,* cattle hair and wool.

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†See Test Your Word Score Page 457.

Beginning with the present study, these patients were asked to observe the skin test sites hourly until bedtime on the day tested and twice a day on the next two days, and to report all reactions. A standard pattern of applying the skin tests was used, and the patient was informed about how to accurately report the reaction to a particular antigen. When any question arose as to the identity of the specific antigen, the tests were repeated.

Patients who reported late reactions were given another appointment for a review of the history with respect to the antigens in question, repeat skin testing if necessary, nasal provocative tests, and nasal smears for eosinophils.

Nasal Challenge

Prior to the nasal challenge the nose and throat were inspected; and the condition of the nasal mucosa, the size of the airway and the amount of mucus in both nares were noted. Mucus from each nostril was taken and placed on separate microscopic slides for staining with Hansel's stain. Then the nasal challenge was performed by spraying 0.15 cc of the suspected antigen directly on the nasal mucosa of one nostril and 0.15 cc normal saline on the nasal mucosa of the other nostril. The patients were not told which nostril received the saline control and which received the challenge. They were observed for 30 minutes and their symptoms recorded. A repeat nose-and-throat examination was performed and the nasal smears for eosinophils were repeated.

Whenever possible, the nasal smears were prepared by having the patient blow each nostril separately onto wax paper. If this procedure did not produce enough material for study, cotton applicators that had been moistened with normal saline were inserted into each nostril for one minute, removed and

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*See Test Your Word Score Page 457.

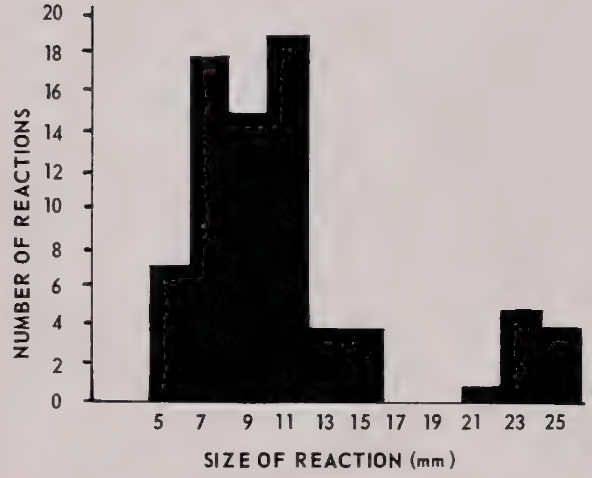

Fig. 1—Size of late reactions in 23 patients.

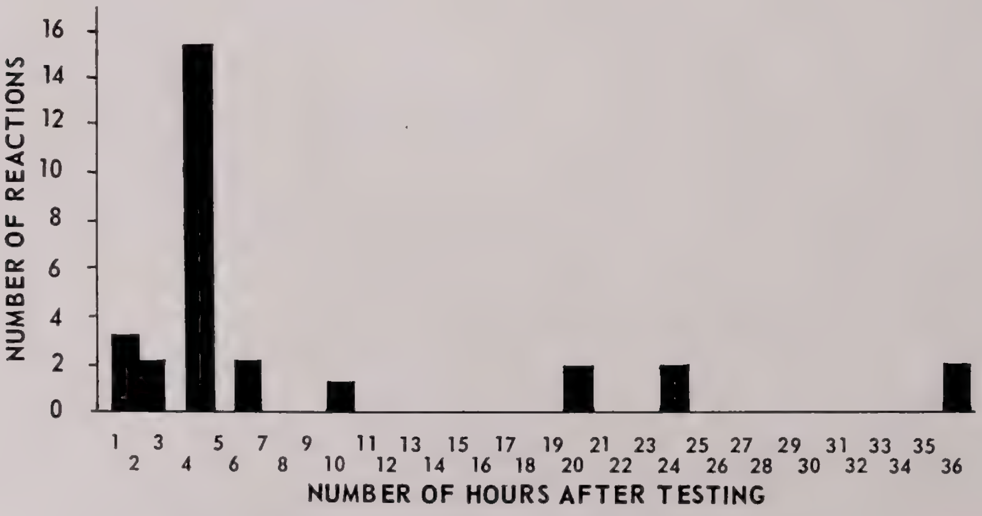

Fig. 2—Number of late reactions by number of hours since onset.

smeared onto microscopic slides. They were then air-dried and stained with Hansel's stain. The patients also prepared slides in a similar manner at home eight and 24 hours, respectively, after the test. Aqueous extracts of pollen and molds were used in a 1:500 dilution and house dust in a 1:10,000 dilution for both the testing and the challenge.

Results

Percentage

The 23 patients who reported late reactions constituted 2 to 3 percent of the group tested during the study interval. The reactions were erythematous papules on an erythematous base; they were moderately pruritic and varied in size from 5 to 25 mm (Figure 1). Of the 77 late reactions in these 23 patients, 52 were in the 6 to 12 mm range. The 23 patients ranged in age from 11 months to 58 years. Six patients were in the first decade, seven in the third, and two each in the second, fourth, fifth and sixth decades. The age distribution of the 10 males and 13 females appeared to be typical of the patients seen in the Allergy Clinic.

Diagnosis

Allergic rhinitis was the primary diagnosis in 18 patients, including two children who were referred because of recurrent otitis media, an apparent complication of the allergic rhinitis. Asthma was the primary diagnosis in the other five patients, although they also had varying degrees of allergic rhinitis. The three to one ratio of allergic rhinitis to asthma was slightly higher than the average in this clinic.

Period of Delay

In 15 patients the late reactions began between the fourth and sixth hours, in three patients between the first and second, in two patients between the second and fourth, and in two patients between the sixth and eighth hours (Figure 2). Other patients had reactions that began at approximately the 10th, 20th, 24th and 36th hours. Three patients had reactions that started at two different times. Ten patients had late reactions only, whereas 12 had both immediate and late reactions (but to different antigens). Several patients showed multiple late reactions, including as many as 15 for some. When the antigens were considered by groups, i.e., pollens, molds, house dust and epithelials, 12 patients reacted to only one group (including five to a single antigen), seven to two groups, and four to three groups (Figure 3). No patients reacted to the four groups. Patients with a single reaction demonstrated no discernible difference by antigen, basic diagnosis and sex from those with multiple reactions. Eighteen patients reacted to molds and, for 11 of them, it was the largest reaction (Figure 4). Twelve reacted to house dust; likewise for five this was the largest. Similarly, seven reacted to pollens and, for four, it was the largest. One patient reacted to cat dander and one to kapok.

The antigens that produced the late reactions corresponded exceedingly well to the clinical history in 13 patients (Figure 5a). In

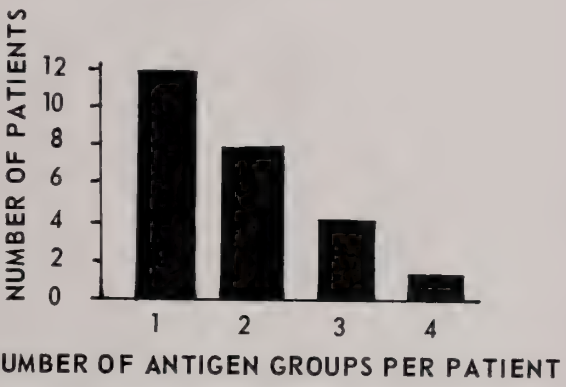

Fig. 3—Number of patients with reactions by numbers of antigen groups.

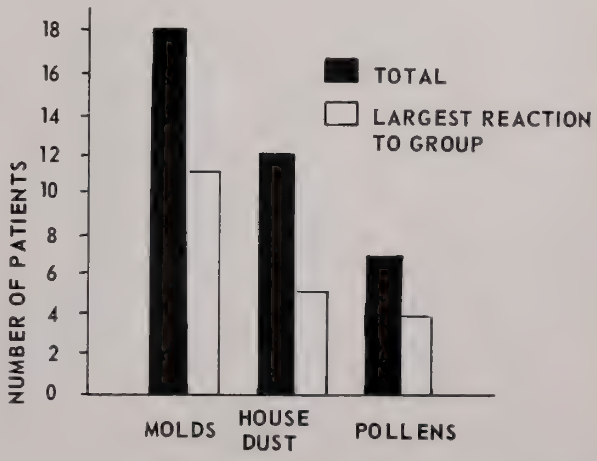

Fig. 4—Number of patients with reactions to various antigen groups.

four other patients, the history was only suggestive. In six the perennial symptoms and the lack of acute observation (usually by the father) made a definite judgment impossible.

Within five to 30 minutes after the nasal challenge, 14 patients complained of significant nasal itching, congestion and/or obstruction and an increase in seromucous rhinorrhea on the challenge side, but not on the control side (Figure 5b). The reactions persisted one to four hours for most patients, whereas they continued 24 to 36 hours for four patients. A few complained of increased itching and tearing of the eyes on the challenge side and/or itching of the palate. No clearcut pulmonary symptoms developed. Those with persistent symptoms did not differ from the rest with respect to antigens, diagnosis, length or course of illness, sex or age.

The symptoms increased in two patients after the challenge, but the effect was almost the same on the control side. One had no change in symptoms, whereas two others had such severe symptoms prior to the challenge that it was impossible to be certain that there was a definite change.

Nasal Eosinophilia

Although the presence of nasal eosinophilia was a consistent finding among these patients, attempts to quantitate the nasal smears were unsuccessful. In those who were asymptomatic prior to the challenge, it was a good index of significant increases in symptoms from the time of the challenge. The smears were positive whenever profuse rhinorrhea was present, but often small increases in counts were difficult to interpret, especially in those with a high percentage prior to challenge or with lower counts that varied from one area of the slide to another. Seven patients had a marked increase in eosinophilia after challenge on the challenge side only (Figure 5c). An increase in eosinophilia in four other patients could not be considered significant. Nine patients were classified as having negative reactions. Three of them had a slight increase in eosinophilia on the challenge side and a similar increase on the control side. Three others who had less than 2 percent eosinophilia before the challenge had a marked increase in the number of lymphocytes and macrophages afterwards, as well as moderate increase in symptoms and rhinorrhea. The remaining three patients were children one, three and five years of age, respectively, with no discernible reaction of any kind to the challenge.

The late reaction of the three-year-old child was entirely different, for it consisted of a 50 to 60 ml patch of eczema beginning approximately 36 hours after the scratch test to Bermuda grass. He had an immediate 18 to 20-ml wheal that lasted three to four hours. The mother reported that during the two previous summers the child had had eczema on the legs and that it was relieved by wearing long pants. Bermuda grass was the only antigen to which the patient reacted, and his allergic rhinitis and asthma attacks were clearly related to ex-

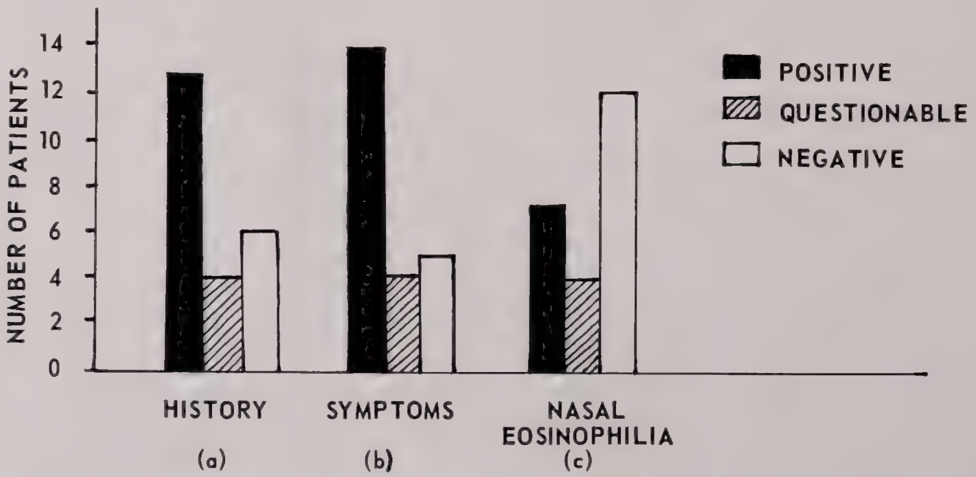

Fig. 5—Positive, questionable and negative correlation of late reactions with history, and with symptoms and eosinophilia after challenge.

posure to that pollen. This child was the only patient who had an immediate and a late reaction to the same antigen.

Physical examination of the patient generally agreed with the symptoms. No patient with a significant increase in symptoms failed to show readily apparent changes on inspection. Two patients with an equivocal increase in symptoms had a marked increase in pallor and edema on the challenge side.

Eighteen of the 23 patients demonstrated excellent correlation between the antigens producing late reactions and *one* of the following: signs, symptoms, eosinophilia after challenge, and history. Two other patients showed highly probable correlations between their antigens and *two* of the four parameters considered. Molds and house dust were the antigens most frequently responsible for late reactions, which usually began from four to six hours after testing.

Discussion

The implication from the results of this study is that the late-occurring reactions are clinically significant. It is now the policy to have all patients who are skin tested at the Allergy Clinic report late reactions. These are considered in the same light as the immediate reaction tests for the treatment of the patient.

Care has been taken to call the reactions late instead of delayed, because in general they appear similar to the immediate wheal and flare responses, and not like the classical tuberculin response, which usually is referred to as delayed. Calling these reactions delayed would add confusion to an already confused terminology and would infer a mechanism that has not been elucidated by this study. One wonders if these reactions might not be mild arthus reactions, but immunologic studies that would confirm or reject this speculation have not been done. It is not known whether the mechanisms for these late reactions are similar to the immediate wheal and flare reactions, in what immunoglobulin fraction the antibody involved in these reactions resides, and how these lesions compare with the classic immediate and delayed reactions.

Conclusions

In a small, but sizable, percentage of allergic patients, local reactions to some or all of the antigens fail to develop until a few hours after intradermal testing. The antigens that produce the late reactions may be highly important to those patients. Therefore, this type of reaction should be looked for actively and given appropriate consideration in evaluations and treatment.

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Poetry and Digestion

I don't know a better preparation for life than a love of poetry and a good digestion.—Zona Gale

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Maternity is a matter of fact; paternity always a matter of opinion.—Ridpath: History of the U.S.

Shakespeare: Diseases

Scrofula (Macbeth)

That "a crew of wretched souls" was delaying the King was the court doctor's reply to Malcolm's inquiry whether Duncan would soon be emerging from the palace.

Those "wretched souls" were scrofulitics suing for the laying on of hands. For centuries English and French kings were supposedly endowed with the divine and hereditary power, "the royal touch," to cure scrofula.* What the doctor himself thought of the ceremonial abracadabra can only be conjectured; monarchs' physicians were too discreet to editorialize on court matters.

When Malcolm asked what disease the doctor was referring to, Macduff explained:

" 'Tis called the evil:†

A most miraculous work in this good king;
Which often, since my here-remain in England,
I have seen him do. How he solicits Heaven,
Himself best knows; but strangely-visited people,
All swollen and ulcerous, pitiful to the eye,
The mere despair of surgery, he cures.
Hanging a golden stamp about their necks,
Put on with holy prayers." Macbeth IV, III

The ritual of the royal touch flourished for centuries, probably initiated by Edward the Confessor early in the eleventh century. Whether or not patients were cured; whether or not they even had scrofula; whether or not they sought the touch for exhibitionism or for the golden disc that was hung around their necks after completion of the rite—all are moot questions.

The royal touch has long been defunct in practice; but under Shakespeare's "magic touch" it survives to contribute literary excellence to Macbeth by way of local color, human interest, and historic validity.

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*Scrofula—from scrofa, a breeding sow, perhaps because of the resemblance between the swollen glands of the disease and little pigs.

†King's evil—tuberculosis of the glands.

Regulation

What's to prevent an occupation that has been granted much autonomy from becoming self-centered and preoccupied with its own interests at the expense of others? With autonomy comes the ever present risk of irresponsibility. The profession must therefore be ultimately subject to social control. . . . The members of every profession know this as well. They try . . . to impose self-regulation partly in order to avoid regulation from without.*

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*Merton, M. K., in Richard Magraw: Ferment in Medicine, 1966.

Treatment of Dog-Bite Wounds

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JOHN F. PAYNE, Major, USAF, MC

IN THE UNITED STATES the problem of dog bite is common. Public health officials estimate that approximately 500,000 to one million persons are bitten each year. Annually since 1957, 50,000 to 60,000 people have received prophylactic anti-rabies injections, averaging 14 injections each.[1]

Wilford Hall USAF Hospital, Lackland Air Force Base, Texas, has a unique source of dog bites because of the presence on the same base of the United States Air Force Sentry Dog School, which uses German shepherd dogs. Physical examinations, isolation of dogs before training, and inoculations eliminate the problem of rabies. However, wounds resulting from bites have been problems, for a dog's mouth is often faster than a trainee's hand.

The inexperienced handler is "wedded" to his dog initially, and they experience a getting-acquainted period. Obedience training follows; similar to the basic training of the human recruit, the dog receives obedience training until his response to commands is virtually automatic. Then the team advances to agitation training in order to develop the aggressiveness that is mandatory for a sentry dog. The person who does the agitating wears padded clothing for protection from the attacking dog. Beyond a certain point of aggressiveness, the handler cannot control the dog, and he may be attached to a stake by a line during such training. Most bites occur during the early period of training, but occasionally also by an over-excited dog in the latter stages.

The characteristics of a dog-bite wound are somewhat involved. Studies by veterinarians at Lackland Air Force Base indicate that the bite power is 150 to 200 pounds per square inch and as much as 400 to 450 pounds per square inch by the end of training. This bite power is adequate at times to perforate the

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sheet metal gauntlet that is worn as a protective device.

The bacterial contamination of the dog-bite wound has been debated. According to some, the saying, "as clean as a hound's tooth," has some validity.[2] Therefore it has been generally taught that these wounds may be cleansed, debrided if necessary, and closed primarily. However, according to the veterinary literature, the nares and tonsils of a dog are a constant source of many organisms. Staphylococcus albus, alpha streptococcus, and Escherichia coli are extremely common,[3] and Staphylococcus aureus, beta streptococcus and Pasteurella septica are also present in significant numbers. Recent studies from the United States Air Force Epidemiological Laboratory at Lackland Air Force Base have shown that the carrier rate of Staphylococcus aureus, as determined monthly among dogs under controlled conditions, ranges from 16 to 71 percent with an average of 32 percent.[4] Penicillin-resistant Staphylococcus aureus ranges from 10 to 16 percent. Because of this source of infection and the force with which these animals attack, the dog bite must be considered as a potential infected crush injury, and not a simple laceration.

Material

Since 1961, 74 dog bites of the extremities were serious enough to require transfer to the Orthopaedic Clinic at Wilford Hall USAF Hospital, the majority having occurred during the past two years, commensurate with the increase in the number of dogs being trained for service in Vietnam. During these two years there was an average of four bites each month; but only patients who had more severe bites were referred to the hospital. Fifty patients were hospitalized; of these 45 had upper extremities involved and five lower extremities. The 24 patients not hospitalized had involvement of the hand or forearm.

Results

One of the most serious problems in handling these wounds arose with the patients initially treated in the emergency room or the outlying dispensary. Thirty patients were hospitalized after receiving initial treatment three or more hours earlier; 14 had wounds that were described at first as puncture wounds of the hands or fingers. Their wounds were cleansed in the emergency room with Phisohex and covered with a simple bandage. From three to 72 hours later, these patients returned for hospitalization, with massively swollen hands or fingers, as well as limitation of motion. On no occasion was an organism isolated from these patients, although three had epitrochlear and one, axillary nodes. All of these patients responded well to simple splinting, ice, elevation, and soaks.

Debridement and Closure

Ten patients with wounds of the hand or forearm were treated according to the precepts of debridement and primary closure. Of these, eight had positive cultures, including three with Staphylococcus aureus, two penicillin-resistant, two with Escherichia coli, one with beta streptococcus, one with Aerobacter, and one with erysipelothrix, Staphylococcus aureus and Escherichia coli. The wounds of the two patients with cultures reported as showing "no growth" were described as erythematous; swelling and drainage also were present. In addition, serious complications occurred in this group. A mid-palmar space infection developed in one patient and required incision and drainage; the flexor tendon sheaths of the fourth and fifth fingers were necrotic. Another patient required suturing of laceration over the left fourth metacarpophalangeal joint. On incision and drainage one week later, the metacarpophalangeal joint was found to be completely destroyed; Staphylococcus aureus was the responsible organism.

Secondary Closure

The remaining 20 patients who were hospitalized had wounds that were allowed to heal by secondary intention; but sometimes they required secondary closure or split-thickness skin grafting. Positive cultures were obtained from six of these patients; Staphylococcus aureus was responsible in three, Aerobactor klebsiella in two, and beta streptococcus in one; none of these patients had complications.

Antibiotics

Those who recommend treating dog bites

as lacerations also advise the use of a broad-spectrum antibiotic or of penicillin. Only nine patients in the present series received antibiotics; eight of these were among the ten patients who had had their wounds closed primarily but had returned later with the wounds infected. Only then were these patients started on antibiotics. The one patient with beta streptococcus was treated with penicillin; only one patient who had a puncture wound was treated with antibiotics, and a comparison with experience in treating similar wounds gave no indication that the antibiotics shortened the period of healing.

The 24 patients who had upper extremity involvement and were treated on an outpatient basis had wounds comparable to the 42 treated as inpatients. Therapy consisted of thorough cleansing, splinting, bulky compressive dressings (Figure), and elevation for two to four days. Then soaks were started, if needed. Although none of these patients received antibiotics, they had no complications.

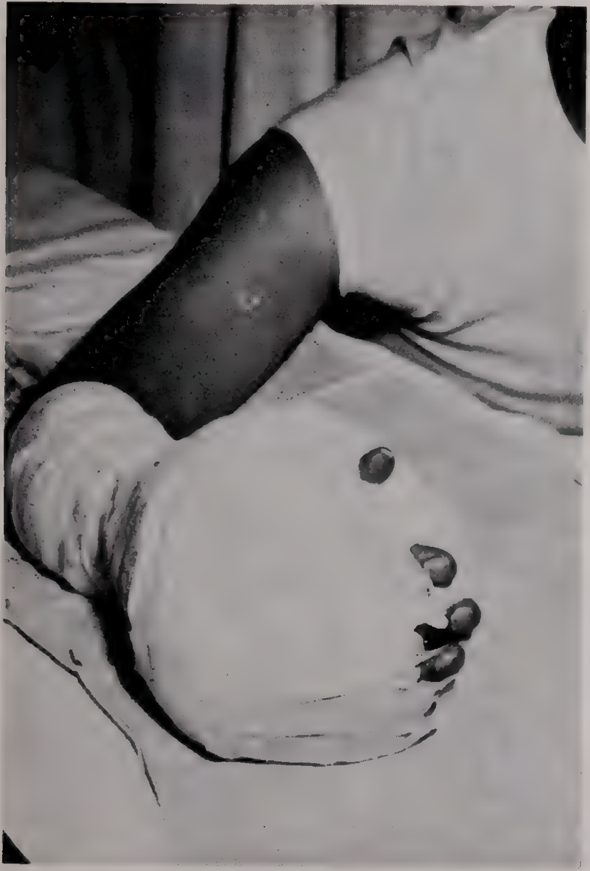

Figure 1—Application of bulky dressing.

Discussion

Dog bites constitute a more serious problem in the United States than is generally realized. It is estimated that from 500,000 to one million people are bitten each year.[1] According to three studies, the extremities have been involved in approximately 75 percent of all bites.[5-7] Actually, the rate of infection in dog bites is unknown. In the epidemiological study of Parrish and associates,[1] the rate of infection has not been determined. Lee and Buhr have investigated 69 dog bites bacteriologically[7] and found an overall infection rate of 29 percent. They report that of the 30 dog bites closed primarily, 47 percent became infected, the most commonly isolated organism being Pasteurella septica. This observation corresponds to the findings of other investigators[8-10] who report complications, such as septicemia and osteomyelitis due to Pasteurella septica. In contrast, 80 percent of the wounds closed primarily in the present series became infected, but no single organism predominates as in Lee and Buhr's series.

Birt[11] reports on 175 dog bites in Great Britain. He states that the most common complication in that country is the development of pyogenic infection; but he includes no percentages in his report. In the United States most authors have dismissed the dog bite as a laceration and advised that the "usual surgical principles" be followed.[2,12,13] However, the present experience demonstrates that the wound must be recognized as an infected crush wound.

Summary

During the past five years 50 patients with dog bites were hospitalized and 24 treated as outpatients at Wilford Hall USAF Hospital. In contrast to treating dog bites as lacerations, as recommended in the current textbooks and journal articles, present experience has dictated the necessity for considering these wounds as infected crush wounds. All patients hospitalized had clinically infected wounds, and the cultures were positive in 20 percent of the patients and became positive in 80 percent of the patients with wounds closed primarily. Two complications resulted in permanent disability in the latter group.

Patients who were treated by thorough cleansing, splinting, bulky dressing, elevation, and soaks had no serious complications. The treatment of this group of wounds was completed by secondary closure and split-thickness skin grafting, or by permitting the wound to close by secondary intention. Antibiotics were not found necessary to the successful treatment of these patients.

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Of The Epidemics—Case XV

In Thasus, the wife of Dealces, who was lodged upon the Plain, from sorrow was seized with an acute fever, attended with chills. From first to last she wrapped herself up in her bedclothes; still silent, she fumbled, picked, bored, and gathered hairs (from them); tears, and again laughter; no sleep; bowels irritable, but passed nothing; when directed, drank a little; urine thin and scanty; to the touch of the hand the fever was slight; coldness of the extremities. On the ninth, talked much incoherently, and again became composed and silent. On the fourteenth, breathing rare, large, at intervals; and again hurried respiration. On the sixteenth, looseness of the bowels from a stimulant clyster; afterwards she passed her drink, nor could retain anything, for she was completely insensible; skin parched and tense. On the twentieth, much talk, and again became composed; loss of speech; respiration hurried. On the twenty-first she died. Her respiration throughout was rare and large; she was totally insensible; always wrapped up in her bedclothes; either much talk or complete silence throughout. Phrenitis.*

—Hippocrates

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*Encephalitis

School of Salernum

Of washing of your hands much good doth rise,
'Tis wholesome, cleanely, and relieves your eyes.
—Regimen Sanitatis Salerni

Editor's note: Though I hadn't thought of it before, the School had a rather subtle, sardonic method of relieving conjunctivitis in the days when murine might have been sea water.

The Management of Rh ISO-Immunization

by Amniotic Fluid Analysis

DALE R. DUNNIHOO, Lt. Colonel, USAF, MC*

SINCE THE DISCOVERY of the Rh_0(D) blood factor in 1940,[1] significant advances in the diagnosis, management and prevention of Rh sensitization in pregnancy have occurred. The primary method of diagnosis is based on the early studies of Bevis,[2,3] who showed a direct relationship between the amount of bilirubin in the amniotic fluid and the severity of the fetal hemolytic process. The subsequent use of amniotic fluid analysis in the management of Rh iso-immunization in pregnancy has resulted in a decrease of the perinatal mortality from approximately 25 to 9 percent.[4,5]

Although a method of prevention[6] is available currently, the present group of sensitized patients in the childbearing ages will continue to provide a challenge to the obstetrician for approximately the next 10 years. During this period, further refinements in diagnostic and therapeutic technics will be necessary if a continued reduction in perinatal mortality is to be realized.

The four factors essential for an accurate assessment of the fetal state are: (1) the individual delta optical density value, (2) the trend of serial delta optical density values, (3) the changes in the bilirubin peak on the spectrophotometric scan, and (4) the changes in the slope angle of the baselines on serial scans.[7,8] The present study is an attempt to define the usefulness of these four factors in determining the condition of the fetus in an Rh sensitized pregnancy.

Material and Method

Wilford Hall USAF Hospital functioned in its capacity as a consultation center for 51 per cent of the patients in this series. Primary management was accomplished at other Air Force installations except for patients with severe involvement who were referred to this hospital. Inasmuch as patients who underwent intrauterine transfusion procedures will be

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the subject of a later report, they were excluded from the present study.

There were 265 amniotic fluid specimens available for evaluation in 85 patients. Amniocentesis was performed from once to 11 times in each patient between 23 and 40 weeks of gestation. The amniotic fluid specimen was placed in a brown bottle immediately after collection and sent to the laboratory, where it was centrifuged for 10 minutes at 2500 rpm and filtered through a No. 48 millipore filter in order to assure removal of all particulate matter. Then the fluid was scanned on a Beckman DK-2A® automatic scanning spectrophotometer from 700 mμ to 350 mμ. The values obtained at 12.5 mμ intervals were plotted on semilogarithmic paper after the method of Liley.[9] The baseline was drawn arbitrarily from 375 mμ to 525 mμ on all graphs, as recommended by Freda.[4] To obtain the delta optical density value (△ O. D.), which represented the amount of bilirubin in the amniotic fluid, the baseline value was subtracted from the peak value at 450 mμ (Figure 1). Then this value was plotted on a modified Liley gestation graph, and the level of involvement ascertained according to the week of gestation. Serial determinations of the delta optical density values plotted at one to two-week intervals were necessary to establish the trend of involvement.

In order to evaluate critically the degree of fetal involvement in the patients studied, the last delta optical density value obtained prior to delivery was plotted on a modified Liley gestation graph, which was subdivided arbitrarily into eight subzones, as follows: the minimal-to-no involvement zone represented by subzones 1 and 2; the moderate involvement zone represented by subzones 3, 4 and 5; and the severe involvement zone represented by subzones 6, 7 and 8 (Figure 2). By use of these subdivisions it was hoped that a clearer definition of the degree of fetal involvement could be obtained from the data.

Results

Three primary types of trends in serial delta optical density values were identified during this study. They were an increasing trend (A), a parallel trend (B), and a decreasing trend (C) (Figure 3). As anticipated, these trends had a tendency to reflect the three basic

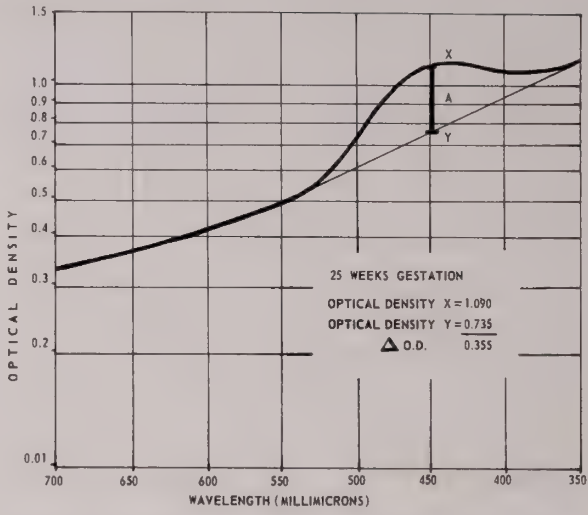

Fig. 1—Semilogarithmic graph showing the method of obtaining the delta optical density value.

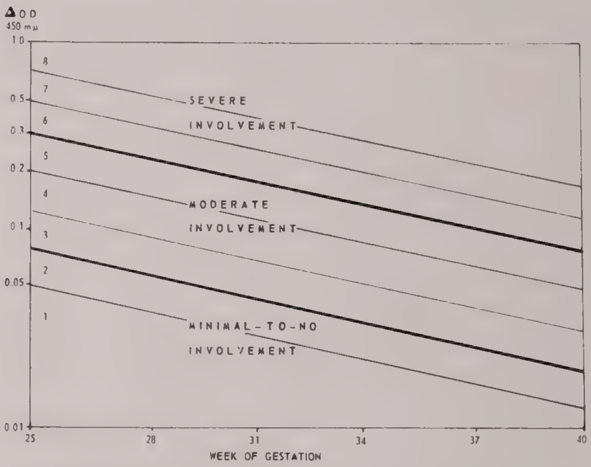

Fig. 2—Modified Liley gestation graph showing the arbitrary division into subzones 1 through 8.

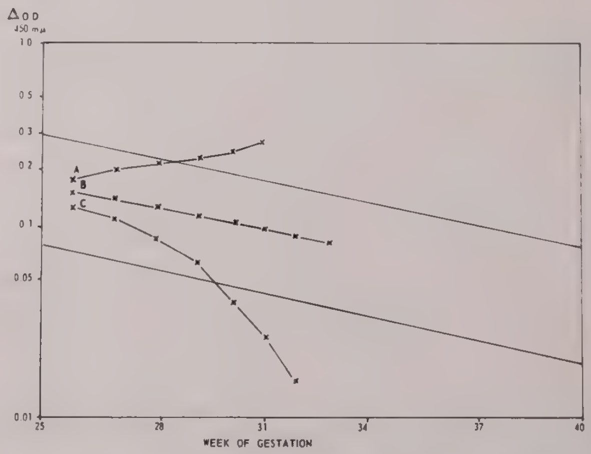

Fig. 3—Three primary delta optical density trends: A, increasing trend; B, parallel trend; and C, decreasing trend.

zones of Liley (Table 1). With the exclusion of the single isolated values, decreasing trends were noted in 88 per cent of the patients in the minimal-to-no involvement zone, parallel trends in 61 per cent of the patients in the moderate involvement zone, and increasing trends in 75 per cent of the patients in the severe involvement zone.

TABLE 1

Types of Trends in Patients in Each Zone of Liley

Zone	Trend		
	Increasing	Parallel	Decreasing
Minimal-to-no involvement	1	2	22 (88%)
Moderate involvement	10	19 (61%)	2
Severe involvement	6 (75%)	2	0
Total	17	23	24

The division of the modified Liley gestation graph into eight subzones revealed a sharp separation of the data with regard to the degree of fetal involvement (Table 2). The average cord hemoglobin value decreased abruptly between subzones 4 and 5. In addition, with the exception of one fetal death in subzone 2 associated with technical difficulties during a neonatal exchange transfusion, no fetal losses occurred below subzone 5. Of the 18 fetal deaths in this series, seven (39 per cent) occurred in subzone 5, the high moderate zone of Liley.

Examination of changes in the spectrophotometric scan that might have prognostic significance revealed that two changes in the bilirubin curve pattern were associated with severe fetal involvement. These changes, previously described by Queenan and Goetschel,[8] consisted of a gradual shift of the bilirubin peak into the shorter wavelengths as the hemolytic process became more severe. The initial shift of the peak to the 420 mμ area produced a double peak at 450 mμ and 420 mμ. Later, immediately prior to fetal death, another shift into the 410 mμ area occurred (Figure 4). A similar shift of the bilirubin peak into the shorter wavelengths may occur in the presence of blood contamination of the amniotic fluid. Oxyhemoglobin produces a major peak at 412 mμ and two minor peaks at 540 mμ and 575 mμ.[7] If blood contamination is minimal, the minor hemoglobin peaks may be difficult to identify and the major peak can be mistaken for the 410 mμ peak of methemalbumin. When methemalbumin is present, a major peak occurs at 410 mμ and a minor peak at 623-630 mμ.[7]

The present series included 11 patients with a bilirubin peak shift into the 410 mμ area that was not associated with fetal death. Only five of these patients had a confirmatory minor peak at 630 mμ, and only two of them had cord hemoglobin values of 8.0 gm per 100 ml or less. For seven of the 11 patients, the cord hemoglobin was less than 11.0 gm per 100 ml.

TABLE 2

Distribution of Patients with Rh Iso-immunization by Zone, Subzone and Outcome of Pregnancy

Zone	Sub-zone	No. patients	Average cord hemo-globin gms%	No. neonatal deaths	No. still-births	Salvage %
Minimal-to-no involvement	1	20	13.7	0	0	100
	2	13	13.9	1	0	92
Moderate involvement	3	13	14.0	0	0	100
	4	13	11.6	0	0	100
	5	13	8.2	4*	3†	46
Severe involvement	6	6	7.1	2	2*	33
	7	3	—‡	2*	1	0
	8	4	—‡	0	3†	25
Total		85		9	9	80

*Includes 1 hydrops fetalis.

†Includes 2 hydrops fetalis.

‡Insufficient data.

In this series there were 18 fetal deaths, nine neonatal deaths and nine stillbirths. Of the 18 deaths, three were not associated with changes in the bilirubin peak, although the delta optical density values for the three were in the severe zone of Liley. In 12 of the 15 remaining fetal deaths there was a definite 410 mμ shift; in nine of the 12 there was also a confirmatory 630 mμ peak, whereas in three, contamination with blood made evaluation of the peak shift impossible. In two of the three with blood contamination a 630 mμ peak was present. Thus, 12 of the 15 patients with scans suitable for evaluation demonstrated a 410 mμ peak in association with fetal death.

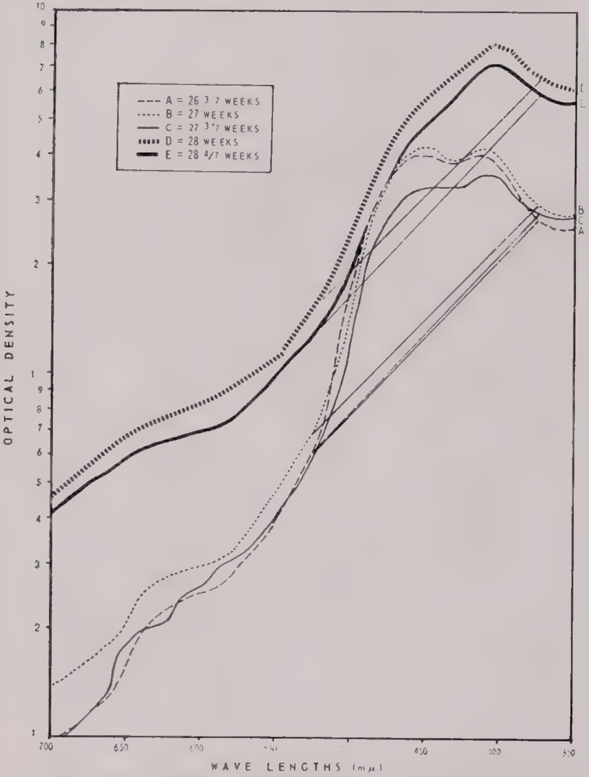

Fig. 4—Serial spectrophotometric scans showing the 420 mμ and 410 mμ shifts in the bilirubin peak. Note the minor peak at 630 mμ on scans A, B, D, and E.

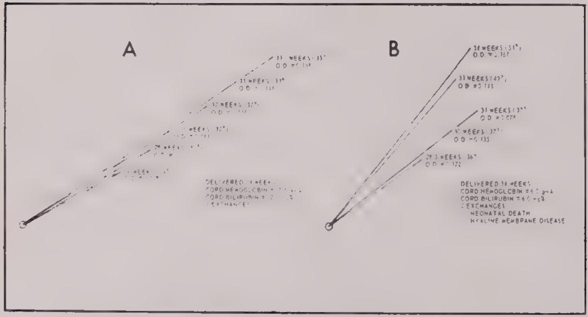

Fig. 5—Comparison of the baseline slope angles in serial delta optical density (ΔO.D.) values of two patients. Patient A had no bilirubin peak shift into the 410 mμ area, whereas patient B had a 410 mμ peak shift.

Another change pointed out by Queenan and Goetschel[8] is that of increased angulation of the baseline on serial scans when the peak has shifted into the shorter wavelengths. When an uninvolved scan was compared to that of a severely involved scan with a peak shift, the baseline was found to have increased as much as 50 degrees from the horizontal. The resultant delta optical density values remained almost constant, even though the hemolytic process became more severe. A comparison of the data in two patients served to illustrate this change (Figure 5). Although the delta optical density values remained about the same in both patients, the slopes of the serial baselines differed markedly. In patient A, with no 410 mμ shift, the slope of the baselines changed little. However, in patient B, with a 410 mμ shift, the baselines increased to 51 degrees from the horizontal. This change in slope of the baselines in patient B masked the severity of the hemolytic process. Therefore, both patients appeared to be similarly involved on the basis of the delta optical density values, whereas patient B was much more severely involved. When the patients were delivered at 34 weeks of gestation, the cord hemoglobin in patient A was 11.6 gm per 100 ml, but the cord hemoglobin of patient B was 6.0 gm per 100 ml.

Discussion

The purpose of this study was to evaluate four prognostic factors in amniotic fluid analysis in 85 patients with Rh sensitization. These factors were: (1) the individual delta optical density value, (2) the trend of serial delta optical density values, (3) the changes in the bilirubin peak on the spectrophotometric scan, and (4) the changes in the slope angle of the baselines on serial scans.

Individual Delta Optical Density

The individual delta optical density value was important in establishing the level of involvement beyond 36 weeks gestation, but prior to this time a single value was of little benefit. Since the magnitude of the curve deviation from normal at 450 mμ decreases progressively as gestation advances in uninvolved pregnancies, it would be essential for a single value to be considerably elevated before it could be considered significant.

Trend of Serial Optical Density

Only after a trend was established could a more accurate prognosis be considered. The trend of serial optical density values was determined by obtaining amniotic fluid specimens at one to two-week intervals and plotting the values on the modified Liley gestation graph. A minimum of three values was necessary to establish a definite trend. If the trend was decreasing, the fetus almost always survived. If the trend was increasing, the fetus was involved to the extent indicated by the zone of involvement, unless there were changes in the scan pattern. Parallel trends were more difficult to evaluate, for they tended to increase or decrease abruptly and assume the prognosis of the subsequent trend. Occasionally, an increasing or decreasing trend would level out and assume a parallel trend.

Change in the Bilirubin Peak

The shift of the bilirubin peak from 450 mμ into the shorter wavelengths was an additional factor in determining prognosis. Although this finding was not limited to a single zone of involvement, the majority of patients with this finding were in the moderate and severe zones of Liley. The significant features of the bilirubin peak shift were the presence of a major peak at 410 mμ, usually associated with a confirmatory minor peak at 630 mμ, and a progressive increase of both peaks on subsequent serial scans. When this occurred, 75 per cent of the infants were significantly involved and 50 per cent did not survive. Considerable caution should be observed in interpreting scans of amniotic fluid contaminated with blood because of the similarity of the 412 mμ peak secondary to oxyhemoglobin.

Freda[4] suggested that the bilirubin peak shift into the shorter wavelengths was caused by fetal acidosis, for the addition of acid to the amniotic fluid produced the same effect. Queenan[7] stated that methemalbumin would produce a major peak at 410 mμ and a minor peak at 623-630 mμ. Abelson and Boggs[10] studied the plasma pigments of infants with erythroblastosis fetalis by spectrophotometric analysis and noted that heme pigments with maximum absorption at 410 mμ or less occurred in infants that usually were severely affected. It would be interesting to speculate that the fetal reticuloendothelial system was overwhelmed by the hemolytic process and that free heme pigment somehow escaped into the amniotic fluid and appeared on the scan as methemalbumin. However, no reliable evidence to support this concept is available at the present time.

Change in the Slope

The change in slope angle of the baseline on serial scans seemed to be significant in its effect on the delta optical density value. Decreasing trends were characterized by a decrease in the slope angle on serial scans from 30 to 40 degrees down to 15 to 20 degrees from the horizontal. Increasing trends had a reverse pattern. Although these changes occurred to some extent with, or without, a shift in the bilirubin peak, the amount of increase appeared to be more marked when there was a concomitant shift of the bilirubin peak into the shorter wavelengths. Only when there was a shift in the bilirubin peak and an increase in the slope of the baseline did the delta optical density value cease to reflect the true state of the fetus.

Summary

Management of Rh sensitization in pregnancy by spectrophotometric analysis of bilirubin in the amniotic fluid has proven valuable and relatively accurate in the majority of patients. Correlation of the bilirubin peak pattern and the baseline slope changes with the trend of delta optical density values should make it possible to increase accuracy.

The incidence of fetal deaths in patients with delta optical density values in the high moderate zone of Liley (subzone 5) was much higher than anticipated. The data suggested that changes in the bilirubin peak pattern and in the baseline slope angles could serve as additional indicators of the degree of fetal involvement. When these changes occurred,

75 per cent of the infants were significantly involved and 50 per cent did not survive.

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It's the Law

Involuntary Blood Sample Admissible*

The Supreme Court of Arkansas ruled that a blood sample, taken from the driver of an automobile without his permission, was admissible as evidence of his intoxication. The laboratory technician took the blood sample without asking the driver for permission and tested the blood for alcohol. The pathologist who analyzed the blood testified that it contained .140 per cent of alcohol when taken and that the percentage would probably have been higher one hour earlier. The driver of the car had been involved in an accident where a pedestrian was killed. He was convicted of involuntary manslaughter partly on the basis of the blood alcohol determination.

Walker v. State, 429 S.W. 2d 121 (Ark., June 3, 1968; rehearing denied July 15, 1968).
The Citation 17:12, October, 1968.

I Chose Medicine

My sister and I decided that we must train ourselves to earn our living, for the family finances were rapidly diminishing and our only hope of a wide and full life, of going out into the big world, lay in our own efforts. There seemed only a few careers open to us—teaching, nursing, the practice of medicine. I chose medicine, not because I was scientifically-minded, for I was deeply ignorant of science. I chose it because as a doctor I could go anywhere I pleased—to far-off lands or to city slums—and be quite sure that I could be of use anywhere.*

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*Alice Hamilton (1896-) in Why We Became Doctors edited by Noah D. Fabricant, M.D., 1954.

War

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Contraindications—Thrombophlebitis, thromboembolic disorders, cerebral apoplexy or a past history of these conditions, markedly impaired liver function, known or suspected carcinoma of the breast, known or suspected estrogen-dependent neoplasia, undiagnosed abnormal genital bleeding.

Warnings—Watch for the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, retinal thrombosis); if present or suspected discontinue the drug immediately.

British studies reported in April 1968[1,2] estimate there is a seven- to tenfold increase in mortality and morbidity due to thromboembolic diseases in women taking oral contraceptives. In these controlled retrospective studies, involving 36 reported deaths and 58 hospitalizations due to "idiopathic" thromboembolism, statistical evaluation indicated that the differences observed between users and non-users were highly significant. The conclusions reached in the studies are summarized in the table below:

Comparison of Mortality and Hospitalization Rates Due to Thromboembolic Disease in Users and Non-Users of Oral Contraceptives in Britain.

Category	Mortality Rates		Hospitalization Rates (Morbidity)
	Age 20-34	Age 35-44	Age 20-44
Users of Oral Contraceptives	1.5/100,000	3.9/100,000	47/100,000
Non-Users	0.2/100,000	0.5/100,000	5/100,000

No comparable studies are yet available in the United States. The British data, especially as they indicate the magnitude of the increased risk to the individual patient, cannot be applied directly to women in other countries in which the incidences of spontaneously occurring thromboembolic disease may differ.

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or sudden onset of proptosis, diplopia or migraine. Withdraw medication if papilledema or retinal vascular lesions are found.

Since the safety of Ovulen in pregnancy has not been demonstrated, it is recommended that pregnancy be ruled out for any patient who has missed two consecutive periods before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule the possibility of pregnancy should be considered at the first missed period.

A small fraction of the hormone agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

Precautions—Pretreatment physical examination should include special reference to the breasts and pelvic organs, and a Papanicolaou smear.

Endocrine and possibly liver function tests may be affected by Ovulen. Therefore, it is recommended that such tests if abnormal be repeated after the drug has been withdrawn for two months.

Pre-existing uterine fibromyomas may increase in size under the influence of progestogen-estrogen preparations.

Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.

In breakthrough bleeding, and all irregular vaginal bleeding, consider nonfunctional causes. Adequate diagnostic measures are indicated in undiagnosed vaginal bleeding.

Carefully observe patients with a history of psychic depression and discontinue the drug if severe depression recurs.

Any possible influence of prolonged Ovulen therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study.

A decrease in glucose tolerance has occurred in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be observed carefully while receiving Ovulen.

Because of the effects of estrogens on epiphyseal closure Ovulen should be used judiciously in young patients in whom bone growth is not complete.

The age of the patient constitutes no absolute limiting factor, although Ovulen therapy may mask the onset of the climacteric.

The pathologist should be informed of Ovulen therapy when relevant specimens are submitted.

Adverse Reactions—A statistically significant association has been shown between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: cerebrovascular accidents, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, breast changes (tenderness, enlargement, secretion), change in weight, changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post partum, cholestatic jaundice, migraine, allergic rash, rise in blood pressure in susceptible individuals, mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme and nodosum, hemorrhagic eruption, itching.

The following laboratory results may be altered by oral contraceptives: hepatic function: increased sulfobromophthalein and other tests; coagulation tests: increase in prothrombin, Factors VII, VIII, IX and X; thyroid function: increase in PBI and butanol extractable protein bound iodine, and decrease in T^3 uptake values; metyrapone test; pregnanediol determination.

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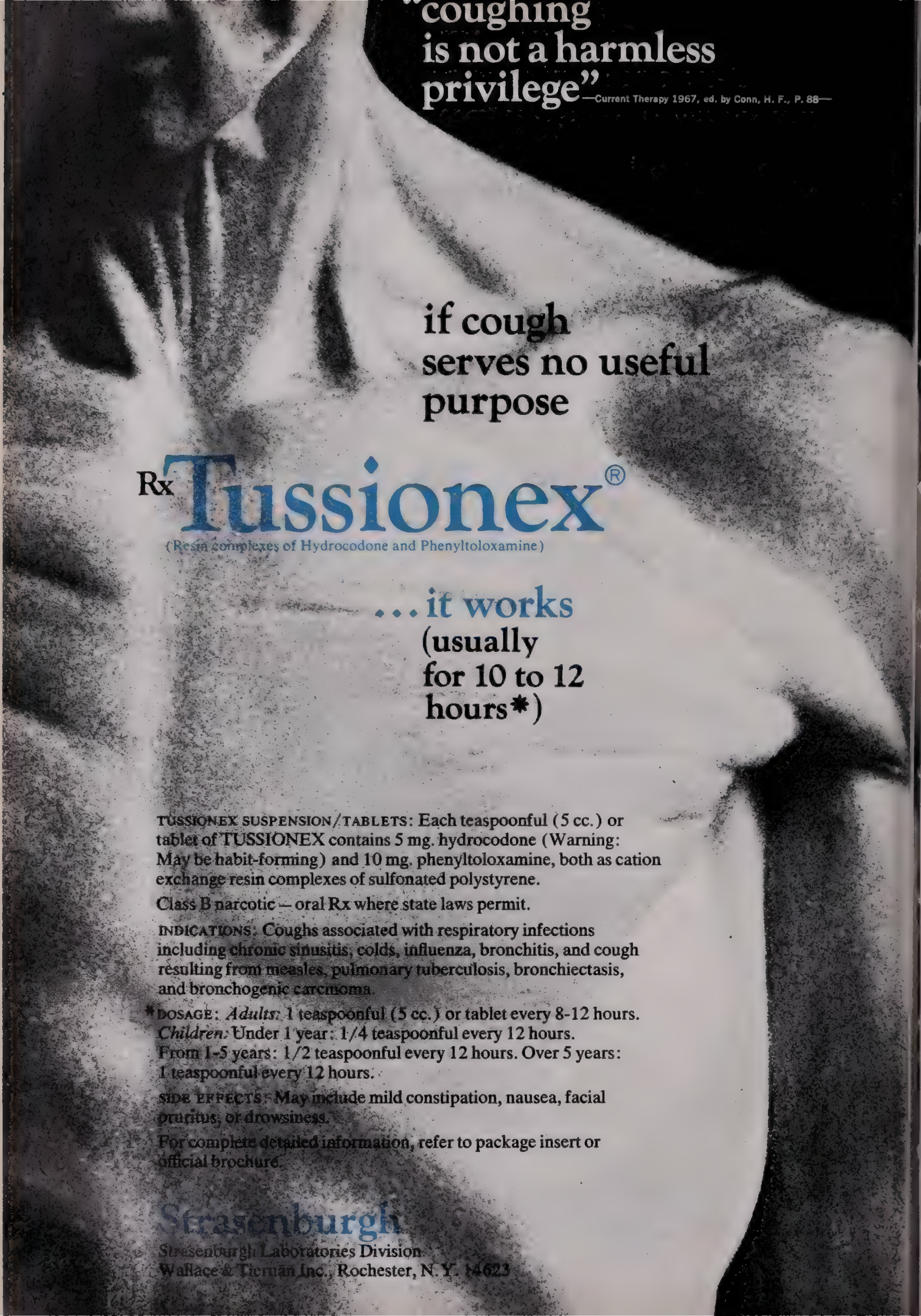

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Editorials

Wilford Hall USAF Hospital

THE EDITORS of MINNESOTA MEDICINE are pleased to present this issue from the Wilford Hall USAF Hospital. Elsewhere in this issue* an account of the development of this huge medical installation is given. General Thomas Crouch assumed command of Wilford Hall Hospital on June 1, 1965; however command changed hands November 1, 1968, and Wilford Hall Hospital is currently supervised by Brigadier General Edgar Harrison Underwood, Jr. General Underwood, in addition to being a flight surgeon, is a member of the Aerospace Medical Association, Society of Air Force Flight Surgeons, and is a Fellow of the American College of Surgeons. Through General Underwood we extend our thanks to the Medical Staff at Wilford Hall Hospital and particularly to the physicians who contributed to this issue of MINNESOTA MEDICINE.

Many members of the Minnesota State Medical Association have pleasant memories of duty at Kelly Field, the site of Wilford Hall Hospital, during World War II. This member of the Board of Editors served as the first medical director of the San Antonio Aviation Cadet Center when it was opened for Cadet Reception in the Fall of 1941. I recall those gruelling days when 300 cadets traipsed through the wooden barracks building assigned to the Medical Department every day, five days a week, for an Air Force physical examination. Those days, of course, the cadets were members of the Army Air Corps, the Air Force not yet in being. Dr. E. G. Benjamin was one of the early physicians in charge of these examinations. The high point of our service together at Kelly Field was a trip we two medical officers took to Ft. Sill, Oklahoma, in the rear seats of two AT-6's. This was a training flight for the pilots and the flight surgeons, and incidentally Ft. Sill was the training location at that time of the Minnesota Hospital Unit.

It is important that the advances in medicine being made currently in military hospitals be made available to civilian physicians. We are pleased to take part in such dissemination of important information.

Reuben Berman, M.D.
Minneapolis, Minnesota

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*See page 541.

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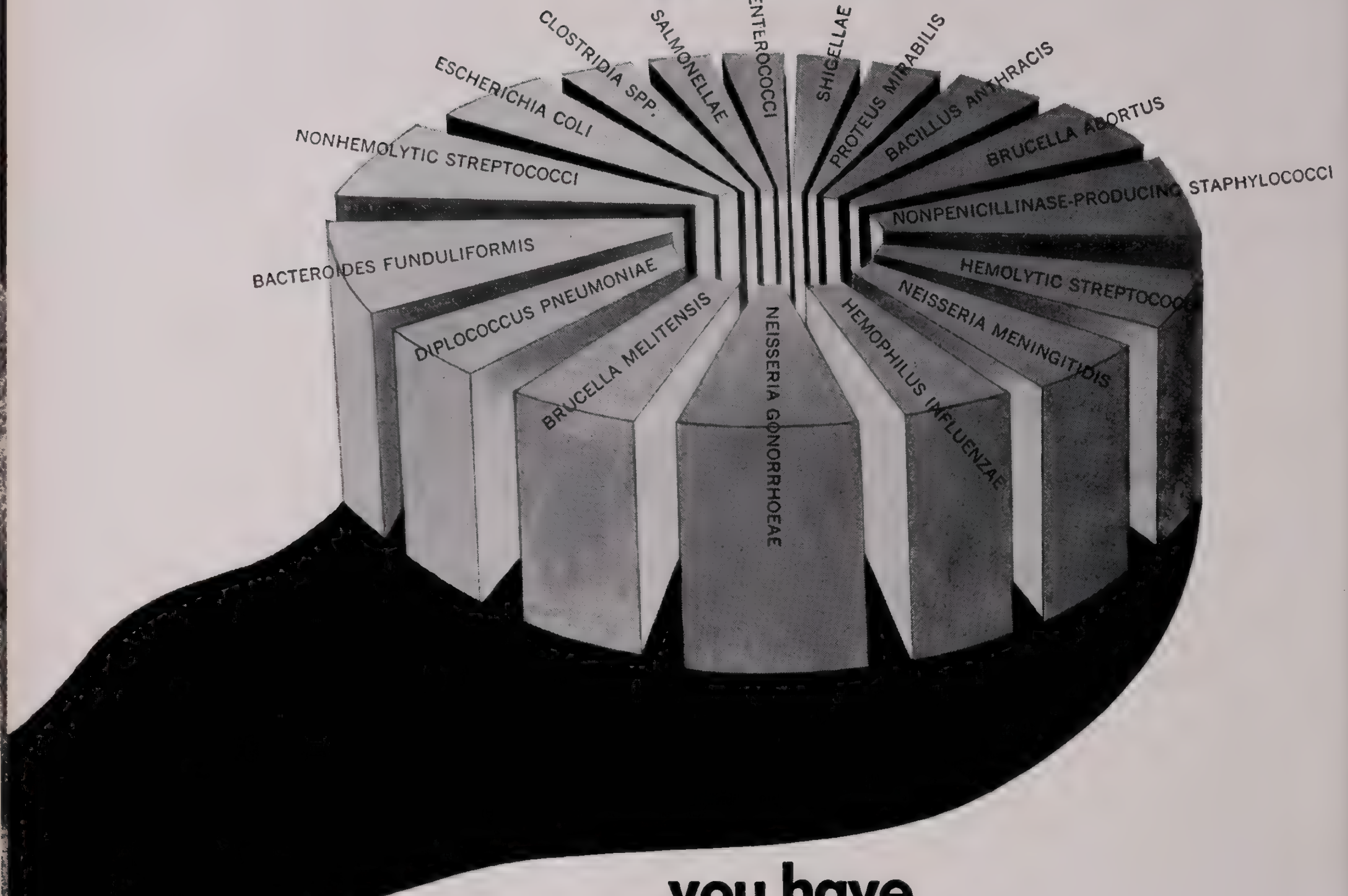
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PRESCRIBING INFORMATION. For complete information consult Official Package Circular. **Indications:** Infections due to susceptible strains of Gram-negative bacteria (including Shigellae, *S. typhosa* and other Salmonellae, *E. coli, H. influenzae, P. mirabilis, N. gonorrhoeae* and *N. meningitidis*) and Gram-positive bacteria (including streptococci, pneumococci and nonpenicillinase-producing staphylococci). **Contraindications:** A history of allergic reactions to penicillins or cephalosporins and infections due to penicillinase-producing organisms. **Precautions.** Typical penicillin-allergic reactions may occur, especially in hypersensitive patients. Mycotic or bacterial superinfections may occur. Experience in newborn and premature infants is limited and caution should be used in treatment, with frequent organ function evaluations. Safety for use in pregnancy is not established. In gonorrheal therapy, serologic tests for syphilis should be performed initially and monthly for 4 months. Assess renal, hepatic and hematopoietic function intermittently during long-term therapy. **Adverse Reactions:** Skin rash, pruritus, urticaria, nausea, vomiting, diarrhea and anaphylactic reactions. Mild transient elevations of SGOT or SGPT have been noted. Black tongue has been noted in some patients receiving the Chewable Tablets. **Usual Dosage:** Adults—250 or 500 mg. q. 6 h. (according to infection site and offending organisms). Children—50-100 mg./Kg./day in 3 to 4 divided doses (depending on infection site and offending organisms). Bacterial menir —150-200 mg./Kg./day in 6 to 8 divided d Children weighing more than 20 Kg. shoul given an adult dose when prescribing o In parenteral administration, children weig more than 40 Kg. should be given an adult Beta-hemolytic streptococcal infections sh be treated for at least 10 days. **Supplied:** Capsules—250 mg. in bottles of 2 100. 500 mg. in bottles of 16 and 100. For Suspension—125 mg./5 ml. in 60, 80 anc ml. bottles. 250 mg./5 ml. in 80 and 15 bottles. Chewable Tablets—125 mg. in b of 40. Injectable—for I.M./I.V. use—via 125 mg., 250 mg., 500 mg., and 1 Gm. Ped Drops—100 mg./ml. in 20 ml. bottles.

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Cardiac Catheterization in the Management of the Acutely Ill Patient

THE TRADITIONAL ROLE of the Cardiac Catheterization Laboratory was to serve as an elective tool to establish an anatomic diagnosis in patients with heart disease. Pathophysiologic measurements were not available. The acutely ill patients were considered too sick for catheterization. Image intensification fluoroscopic equipment, rapid methods of pressure and cardiac output measurements, continuous monitoring, techniques for the control of arrhythmias, and advances in resuscitation have expanded the role of the laboratory by enabling the safe and successful catheterization of critically ill patients and have provided pathophysiologic data which may assist in their management. The laboratory may be employed in one of three ways: as a diagnostic tool; to assess and follow pathologic physiology; and as a means of therapy.

The diagnostic catheterization of critically ill patients carries a higher risk[1] than the usual diagnostic study. This fivefold increase is warranted where adequate therapy, e.g., surgery, depends upon a precise anatomical or physiologic diagnosis, for the risk of deferred or improper therapy is greater than that of catheterization. Pulmonary embolism, for example, is a disease where selective pulmonary angiography can establish the diagnosis in patients with obscure clinical pictures or can show the exact localization of the lesions for emergency surgery such as the Trendelenberg procedure. The less hazardous, less time-consuming, but not specific chest films or radioisotope scans can be used to follow the patient once the diagnosis is established.

In the patient with a dissecting aneurysm, aortography will establish the diagnosis and outline the anatomy of the lesion so that the surgeon may be properly prepared to deal with the specific vascular lesion. In the cyanotic infant, conditions such as transposition where prompt surgery may be lifesaving can be differentiated from tetralogy where careful medical management will enable survival so that the defect may be repaired later at lower risk. The postoperative heart surgery patient may benefit from catheterization since defective function of prosthetic valves or grafts, intracardiac clots, faulty repairs, etc., may be demonstrated, enabling prompt surgical correction.

The value of assessing the pathophysiologic changes is best exemplified by the patient in shock. Though presenting a well defined clinical syndrome, these patients may suffer from a diversity of pathologic alterations in cardiovascular physiology, including cardiac output, peripheral vascular resistance and central filling pressure. Catheterization, with measurement of these variables, provides a better understanding of the "shock syndrome" and enables therapy to be directed at the specific alteration. Already a number of shock units have been established to enable physicians to rapidly insert right and left heart catheters and make repeated measurements of these fundamental derangements in patients in shock.

The introduction of catheter pacemakers has demonstrated the importance of the cardiac laboratory in treating certain conditions. The prompt placement of an emergency pacemaker catheter may be lifesaving in a patient with myocardial infarction who develops heart block or in the patient with Stokes-Adams attacks. Pacing is more practicable than drug therapy and produces fewer complications. The laboratory later may be the source of definitive therapy with insertion of a permanent transvenous pacemaker if required.

The introduction by Rashkind[2] of ballooning the atrial septum in patients with transposition of the great vessels to provide better mixing may significantly improve survival in these critically ill infants without the risk of a thoracotomy, another therapeutic use of catheterization. A still newer therapeutic application is the use of pulsed balloon catheters[3] to support the circulation in patients with myocardial failure due to acute infarction, a procedure whose value needs to be further explored.

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in the management of the critically ill patient is already apparent. Its more widespread use depends on the development of techniques which enable the safe, rapid and simple acquisition of data with minimal trauma to the patient, the widespread use of portable image intensifiers so that the laboratory can be brought to the acutely ill patient rather than vice versa, and the use of computer techniques so that the multiple variables present can be rapidly analyzed and the data made immediately available.

Eliot Schechter, Lt. Colonel, USAF, MC
Chief, Cardiology Service

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The United States Air Force Central Tumor Registry

MAJOR AIR FORCE HOSPITALS throughout the United States have had tumor registries for the past seventeen years. Eleven such registries had been functioning, but several inevitable problems had developed from this situation. With the mobile population of Air Force personnel, many patients were followed by three or four tumor registries for the same tumor. In other instances, a patient might move to a new station and be lost to follow-up. Clinical investigation of a particular tumor Air-Force-wide was impossible. Records from each registry were kept locally with the result that an investigator either had access to only a single registry's experience, or would have to make trips to each of the eleven registries to accumulate all of the Air Force data.

In June 1967 a USAF Central Tumor Registry was established to avoid duplication of patient follow-up and loss of patients to follow-up, to assess a quality control of treatment of malignancies in various Air Force hospitals, and to allow physicians access to Air-Force-wide experience. This registry collates the records of the prior registries and incorporates subsequent Air Force records. To accomplish these aims, a new Air Force directive was written requiring all hospital registrars to send copies of pertinent patient material to the Central Tumor Registry each time a patient is admitted to a hospital. Registrars receiving records of patients with malignancy at the time of transfer to a new station are required to register the name and address of such patients with the Central Tumor Registry. All Air Force pathologists, pathology centers and the Armed Forces Institute of Pathology send duplicates of pathology reports of malignant conditions occurring in active-duty, dependent, or retired Air Force personnel. Radiation treatment centers and tumor boards submit duplicates of treatment records and recommendations to the Central Tumor Registry. Physicians caring for patients in the Outpatient Clinic are contacted for their evaluation of the status of patients periodically. By means of these multifaceted checking procedures, almost 100 percent follow-up of patients with malignant diseases is possible.

The functional format of the Central Tumor Registry has been developed to store and code information in a mode that allows total ac-

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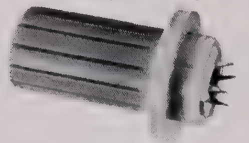

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cessibility and rapid retrieval to all contributing physicians and hospitals. To accumulate information without using it, or to serve merely as a repository of patient records is a useless and wasteful exercise, too often indulged in by tumor registries.

The information in the Central Tumor Registry is accessible to rapid retrieval in two major forms. All records are microfilmed and filed according to tumor type and site. Review of Air-Force-wide experience with a specific tumor may be accomplished readily through diazo duplication ("microfiche") of the contents of the original jacket. Thus a particular hospital's experience can be evaluated, for the microfilm records are filed and accessible in this manner. Specific information about a particular patient or type of tumor, a tumor treated in a certain manner, results of chemotherapy or radiation therapy on longevity and quality of survival, and gross survival statistics are instantly available through a code system using punch-card data sorting or a magnetic tape computer retrieval. Presently, the Central Tumor Registry is collaborating with a non-profit research computer organization (MITRE) to determine the feasibility of computerizing patient data in malignant diseases. The Central Tumor Registry has an "on-line" remote teletype linked to a computer in Massachusetts that allows local program development and nearly instant readout of information from the magnetic tape 2,000 miles away. Information about any of the problems mentioned previously can be obtained, analyzed, calculated statistically and typed in any desired format in five minutes.

At the present time, a physician who wants to use Central Tumor Registry information has access to complete records of any type of tumor or hospital information that he would like to have within 24 hours. If specific information is desired, such as that available on punch cards or magnetic tape, it is retrievable within a few hours. It is hoped that this rapid accessibility will encourage physicians and hospitals to use the tumor registry data rather than consider the register a one-way street on which all information comes into the Central Tumor Registry, only to lie dormant and unused.

Future plans include further development and refinement of the punch-card data, magnetic tape input-accessibility, and further definition of the exact type of computer best suited to registry requirements. It is envisioned that within two years a Phase II computer will be rented for the tumor files. At that time "on-line" teletypes should be available to each major Air Force hospital tied in with the computer in order to allow these hospitals identical accessibility to all Air Force records without having to query the Central Tumor Registry for feedback of information. This registry is only in its first year of development, but the number of patient records available, the refinement of data accessibility and the potential for improvement of patient management have made this hospital most enthusiastic about its future.

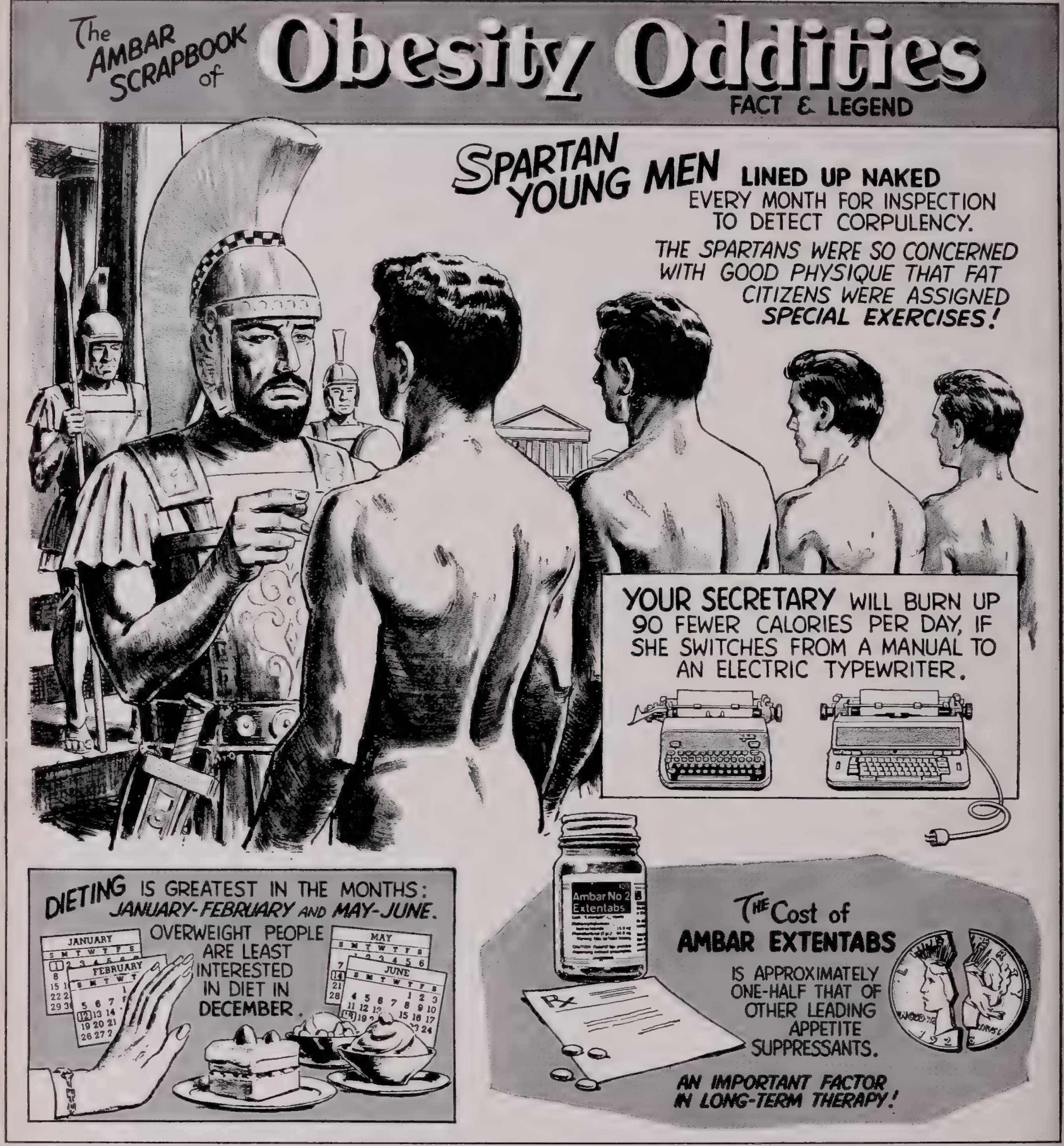
Fred G. Conrad, Lt. Colonel, USAF, MC
Chairman, USAF Central Tumor Registry

Life

Surgeons should be careful
When they wield the knife!
For underneath their fine incisions
Lurks the culprit—Life!
—Emily Dickinson

Serve and thou shalt be served. If you love and serve men, you cannot, by any hiding or stratagem, escape the remuneration.—Emerson

If a man look sharply and attentively, he shall see Fortune; for though she is blind, she is not invisible.—Bacon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Changes in Vietnam Casualty Management

ALTHOUGH MUCH of the surgical management of war wounds in Vietnam is patterned after the lessons learned during World War II and especially during the Korean War, some changes are in evidence. These changes are due to medical advances and to certain aspects of the tactical situation. Helicopter evacuation from the field to definitive treatment centers had its inception during the Korean War. In Vietnam it has become commonplace and, as a result, patients frequently are operated upon within an hour after wounding.[1] Many more patients are thus salvaged, whereas formerly they would have succumbed during the longer interval between injury and treatment required for surface vehicle evacuation.

As a consequence of this expeditious treatment, the postoperative management of many patients who survive with multiple, extensive injuries has assumed more complexity. Therefore, even a slight improvement in the mortality rate among treated Vietnam casualties, compared to that of the Korean War,[1] is a tribute to not only the effectiveness of the helicopter evacuation system, but also, notably, the medical advances in techniques of resuscitation and management of shock.

The cause of missile injury in Vietnam has changed significantly compared to World War II and the Korean War.[1,2] In the latter conflicts, 75 percent of the battle casualties resulted from fragmentation injury and 25 percent from gunshot wounds. However, in Vietnam the incidence of high velocity small arms fire has been close to 50 percent, the difference probably due to the increased number of search and destroy missions during which the individual is more exposed to sniper fire. The significance of a high velocity bullet wound in terms of morbidity has been brought out by a study of 621 Vietnam casualties with penetrating wounds of the abdomen admitted for interval care to the United States Air Force Hospital at Clark Air Base between July 1965 and December 1966.[2] The injury was caused by bullets in 310 patients and by fragments in 311 patients. An abdominal re-operation has been required in 41.3 percent of those with bullet wounds, whereas such intervention was needed in only 13.2 percent of those with fragment wounds. Moreover, 70 percent of the 415 significant complications recorded for the entire group occurred in patients with bullet wounds.

The incidence of arterial wounds in Vietnam is essentially the same as in the Korean War and World War II; however, the management of these injuries has undergone significant changes with each conflict. In World War II the vast majority of arterial wounds were ligated. In Korea, direct arterial suture was introduced and the technique refined. When primary anastomosis was impossible, arterial homografts were used sparingly. Eventually experience was gained in the insertion of a limited number of autogenous vein grafts, which comprised less than 15 percent of repairs in any of the series reported. In Vietnam, vascular repair has been attempted in all patients when there is a potential for salvage of the limb. However, a notable difference in management has been indicated by the significant increase in use of autogenous vein grafts, which constitute approximately 42 percent.[1,2,3]

In general, the more extensive arterial wounds will require vein grafts for reestablishing continuity; however, this correlation has not always been clearly defined. It is possible that the current increased incidence of high velocity small arms fire, with its greater destructive potential, is an apparent explanation for the increased use of vein grafts in Vietnam. However, no correlation has been found between the selection of a vein graft and the wounding agent in 171 major arterial wounds of the extremity.[2] Although it has not been substantiated, it is presumed that, in some cases at least, the selection of vein grafts in Vietnam has reflected a familiarity with this technique gained in recent years during the management of peripheral vascular occlusive disease. The final chapter on vascular injury in Vietnam awaits the results of comprehensive

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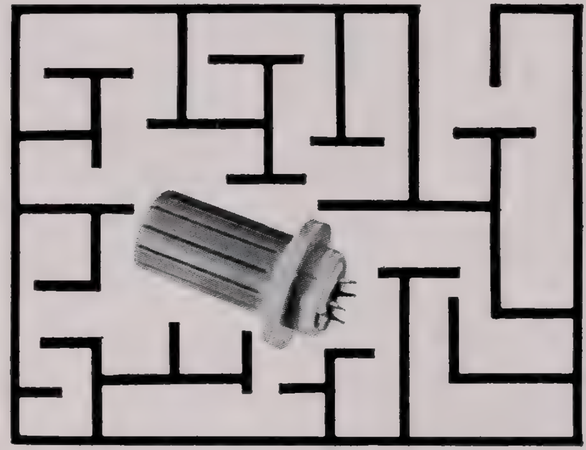

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and exhaustive studies by Rich and Hughes, who have established a Vietnam vascular registry at Walter Reed Army Hospital.[4] Currently, there are more than 850 registered casualties.

The most notable change in the management of thoracic wounds in Vietnam is the use of a chest tube in the treatment of hemothorax and hemopneumothorax.[5] In 77 percent of 476 patients with penetrating wounds of the thorax, insertion of a chest tube was the initial treatment. In marked contrast, thoracentesis was used initially in 80 to 90 percent of patients during the Korean War. Moreover, the incidence of empyema was significantly less in the Vietnam series than in Korea.

An ingenious innovation that combines simplicity with safety is the one-way flutter valve developed by Heimlich,[6] a device which eliminates the need for underwater seal drainage in many patients, often allows earlier ambulation, and permits safer and easier management of patients who must be evacuated to rear echelon treatment centers while a chest tube is in place.

These examples highlight some of the major changes in treatment and management currently practiced in Vietnam. The majority of the principles of casualty care are well established and applied in one conflict after another. However, the overall management can be expected to undergo useful modifications in keeping with advancements in medicine.

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Clinical Research at Wilford Hall USAF Hospital

A NECESSARY COMPONENT to any teaching hospital or teaching program is a research laboratory. The need for an experimental surgical/anatomy unit for the surgical specialties is obvious. An anatomy laboratory is strongly recommended for all surgical residency programs to develop new surgical techniques or to acquire skills in accepted, but difficult procedures which should be practiced on experimental animals to develop speed, assurance and technique. Non-surgical specialties should also have access to a research laboratory as an incentive in acquiring and maintaining the interest of outstanding attending physicians and to induce a high caliber of trainees to select a residency through the assurance that the teaching staff is current in knowledge, active in the forefronts of medical specialties and expert in specific facets of their specialty. If members of the staff have published a great deal and are recognized authorities, young men will be attracted to seek further training under such mentors.

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Some of the more notable achievements accomplished in this laboratory over the past several years have included *pressor assay determinations* as a means of selecting patients with correctible unilateral renal hypertension. McPhaul[1] and his associates with the collaboration of Dr. Arthur Grollman developed and evaluated pressor substance obtained from renal vein plasma in an attempt to correlate the presence or absence of pressor substance with other functional and morphologic parameters of unilateral renal disease and with response following surgical correction of a vascular abnormality or extirpation of a diseased kidney.

In the field of hematology, Conrad and Grisham modified the thromboplastin generation test and thereby detected large numbers of patients with plasma thromboplastin antecedent deficiency (Factor XI).[2] Their publication defined the inheritance, incidence and diagnostic laboratory parameters of this disorder. Cooper's[3] studies on exercise physiology and physical conditioning has revitalized the entire health program of middle-aged Americans.

The publication "Aerobics",[4] which arose from these studies in exercise physiology conducted in the clinical research laboratory, has placed exercise and physical conditioning on a firm scientific basis and will be the standard for Air Force physical conditioning tests.

Most recently, interest has been centered in the area of organ transplantation. Renal homotransplantations, first experimentally perfected in the laboratory, have been performed clinically for the past four and one-half years at Wilford Hall USAF Hospital with notable success.[5] The development of *immuno-suppression techniques,* including thoracic duct fistulae, antilymphocyte globulins, and extensive histocompatibility typing, is being actively investigated. Surgical techniques for cardiac and liver transplantation are currently being perfected by the surgical staff.

The concept of research physicians available to support and to complement clinical specialists as exemplified in the Aerospace Medical Laboratory (Clinical) has proven a successful means for each physician to contribute toward continual improvement in patient care.

Fred C. Conrad, Lt. Colonel, USAF, MC
Director
Aerospace Research Laboratory (Clinical)

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America

Our country, right or wrong. When right, to be kept right; when wrong to be put right.—Carl Schurz

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Atomic energy is like a woman, you can recognize its power even if you can't understand it.—Burton Hillis

"If a free society
cannot help
the many
who are poor,
it cannot save
the few
who are rich."

John F. Kennedy, Inaugural Address

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Abortion or Compulsory Pregnancy?

"The dogmas of the quiet past are inadequate for the stormy present"—Abraham Lincoln

MINNESOTA'S ANTIQUATED abortion law should be repealed or liberalized. The present law, last changed in 1886, was established at a time when women played a far more subservient role in society and had little or no influence on law-making—even that having to do with their own bodies. If *men,* being the law-givers, were the child-bearers and child-tenders in our society, all proscriptions on abortion would undoubtedly have been removed centuries ago.

The question whether abortion is moral or immoral has been strongly colored by generations of philosophers and theologians (all men) indoctrinated in the ancient role of male dominance, and it is their sonorous voices that have established our present punitive abortion laws. Our present law impresses the philosophy of a minority upon all our women. Now that the battle for women's rights has been joined by both men and women, the existing laws relating to abortion are gradually being modified. Recent polls disclose a desire on the part of both the general public and the medical profession for a more humane and liberal law.[1,2,3,4,5] Hopefully, the day will come when a decision regarding abortion will be left to the pregnant woman.

We must ask ourselves who is best qualified to decide whether a pregnant woman should be allowed an abortion? Should the physician alone make this decision? Or the patient's minister, lawyer, or (perish the thought) the pregnant woman herself? An increasing number of countries have answered this question by accepting the premise that the pregnant woman be granted this prerogative.

The unfairness of the present situation is also reason for change. It is unjust that one woman, because she is *poor,* be denied an abortion, while a *wealthy* woman flies to Tokyo, has her abortion performed by a Harvard-trained gynecologist, and is back in Minneapolis within the week. It is unfair that one woman, because she doesn't know the right doctor, be denied an abortion, while another more knowledgeable woman finds a sympathetic physician, here or in a neighboring state, to perform her abortion. It is not only unjust but cruel to hear of a district attorney who commanded a rape victim, under threat of criminal prosecution, to bear the child of her degenerate attacker,[6] when we know, law or no law, that an influential woman could easily obtain an abortion in such a situation.

Should the law be liberalized, medical developments will provide physicians with further indications for abortion; amniocentesis is now being used to determine the presence of a fetus with chromosome abnormalities. This method, in conjunction with a liberal abortion law, would allow us to decrease the percentage of children born with congenital anomalies.

There has been an unnatural concern of many over the "rights of the fetus." The author, while respecting the right to hold such a view, feels that there has been *too little* concern for the pregnant woman. At our own feet must lie some of the responsibility for women who have died following

New drugs take exams, too.

Today, virtually every medical school in the United States cooperates with pharmaceutical manufacturers in the clinical evaluation of new and promising drugs. Just as you might find it significantly more difficult to practice medicine without the useful new compounds made available through original pharmaceutical research in the past twenty years—prescription-drug manufacturers would find it equally difficult to obtain extensive, long-term, dependable evaluations of new therapeutic agents without the close cooperation of medical staffs and clinical facilities of medical schools and teaching hospitals. Such cooperation leads toward more effective care of more patients—the common goal of medical and pharmaceutical research—toward reduction in the cost of disease, toward increase in useful longevity.

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criminal abortions. We cannot be proud of conforming to a law that has produced so much heartache. If we as physicians were truthful regarding our own foibles, we would admit, I think, to a tendency to be *judgmental* in regard to many of the decisions we make. As one woman so aptly stated, "Physician, heal thyself; your deity complex is showing."[7]

In an enlightened society we should, so far as possible, provide conditions that ensure that every child is a wanted child. Unloved, unwanted children are an expensive social burden, for they are unhappy individuals frequently involved in delinquency. Those who snivel about the "rights of the fetus" might better be concerned about the right of every child to a home where he is wanted and loved. Single women who decide to raise an unwanted illegitimate child usually must work; the child is frequently neglected and sometimes even rejected by the mother. Bringing into the world an unwanted child should be recognized for what it is: a crime against the child and society.

Finally, one of the strongest arguments for a more liberal law is the increasing disregard of the present law by so many physicians. Abortions performed to interrupt conception following rape, incest, and German measles are all criminal under the present law. Likewise, abortions performed to help preserve the emotional health of the mother or the stability of the family are also illegal. When it becomes necessary to break the law in order to practice good medicine, then it is time to change the law.

Robert B. Benjamin, M.D.*
St. Louis Park, Minnesota

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*St. Louis Park Medical Center.

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Test Your Word Score

Causalgia—*a burning pain. From kausos (heat) and algia (painful condition)* (page 404).

Atopic—*characterized by atopy: a form of hereditary hypersensitivity, not occurring in lower animals* (page 421).

Spondylocladium—*a genus of fungi, such as cause scurf on potatoes* (page 422).

Fusarium—*a genus of fungi, such as cause dry rot on potatoes* (page 422).

Aspergillus—*a genus of fungi, such as cause fermentation* (page 422).

Phoma—*a genus of fungi, such as cause fruit rot* (page 422).

Kapok—*silky fibers investing the seeds of the silk-cotton tree, used for mattress stuffing* (page 422).

Chromophobe—*a non-staining cell* (page 492).

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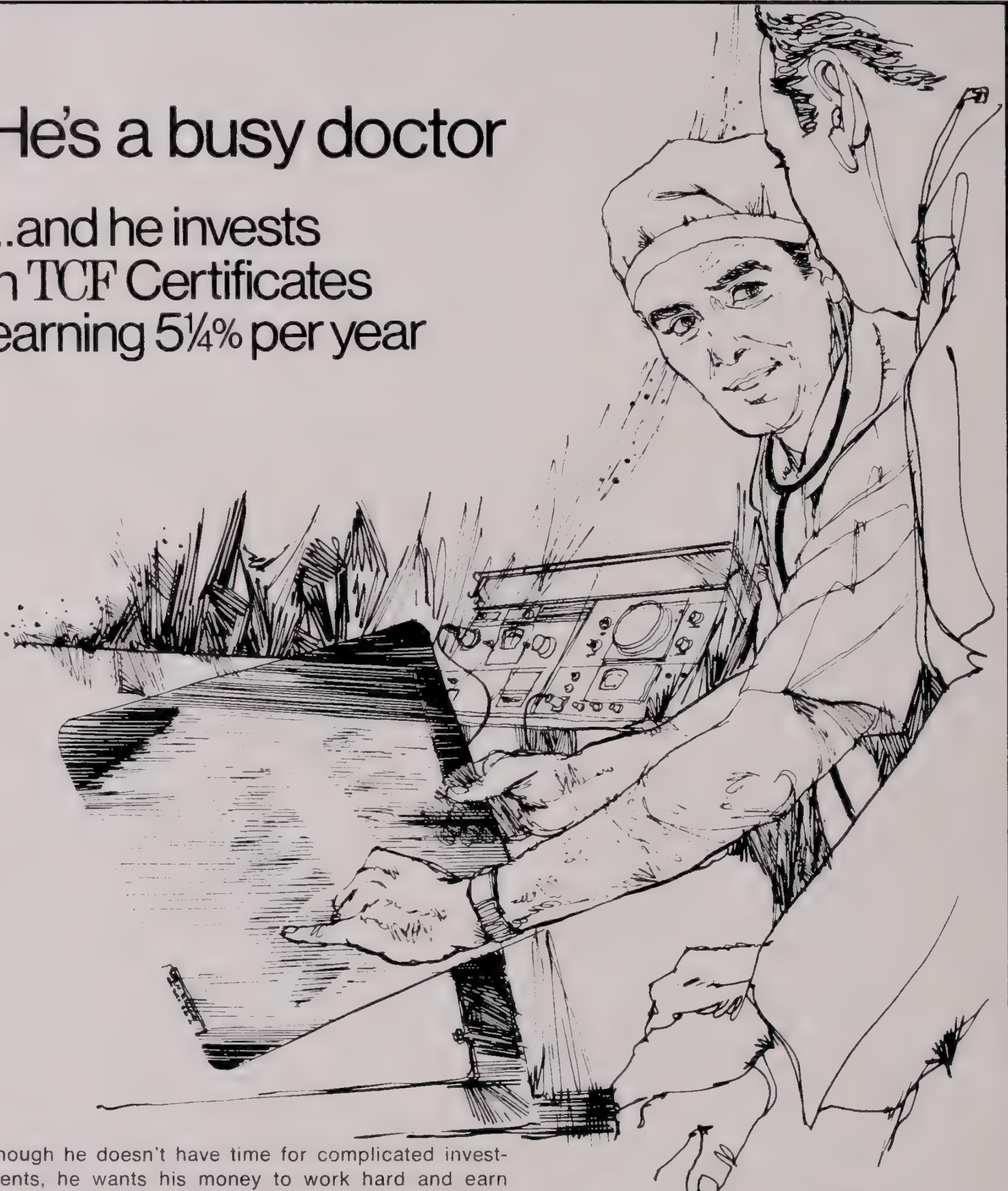

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Letter to the Editor

Isoteric

Dear Editor: Though a non-hunter myself, I found your article in Minnesota Medicine* on "Headaches in the Hunting Season in Kandiyohi County" challenging and informative. Particularly fascinating was the description of the double blind experiment. Though the METHOD was not completely explained, I assume in this case the double blind faced a slough or bog or lake and contained two hunters. Is this not a dangerous experiment in a double blind, both hunters having guns? Please give us more particulars.

Rabbi ben Jacob

Editor's Note: Dear Rabbi ben Jacob, You are so right! You, being a non-hunter, I marvel at your insight in having been able to so accurately decipher the literary implications in my time-consuming scientific venture. As one of the participants in the double blind, I must admit that I had to duck a few times, but fortunately my assailants were amateurs, poor shots, and inadequately equipped; they made my head ache, occipitally, though, and that's what tipped the balance so overwhelmingly in favor of—.

Associate Editor's Note: Now go back and read 'em all. R.B.

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*Minnesota Med 51:1759, 1968.

Dear Colleague Rice!

Through your kindness and open-mindedness, which we gratefully acknowledge, it has become possible to publish in Minnesota Medicine a first, albeit short, cross-section of scientific endeavors in a German University, i.e., in the Department of Surgery of the University of Bonn.

My co-workers and I are grateful for your cooperation in publishing these scientific contributions in Minnesota Medicine at this time and for others in the future. This will broaden the common basis for continuing scientific research and publications; it will deepen our personal and scientific contacts, extend the stream of intellectual exchange, and thus help our mutual scientific endeavors.

The special issue* devoted to the Rheinischen Friedrich-Wilhelms-University in Bonn depicted on its cover a superb picture of our new building of the Surgical Hospitals and Policlinic. For this distinction I would like to add the expression of grateful appreciation of the Dean of my faculty as well as of the Rector of the Rheinischen Friedrich-Wilhelms University in Bonn.

You may be assured that my co-workers and I at the Surgical University Hospitals in Bonn will continue to submit to Minnesota Medicine contributions of our own as well as papers of value as they originate in Germany at large.

My special appreciation goes also to all those responsible for the superb translations as well as for the excellent printing and the layout of the format.

With all my good wishes, also for the New Year, and my best greetings as a colleague, I remain

Director o. Prof. Alfred Gütgemann, M.D.

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*November Issue.

Never before has the fate of so many been at the whim of so few.—Minneapolis Tribune.

Maybe you owe money to banks, stores, companies or people.

We're in debt to wars, floods, health services, life saving and blood banks.

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The Editor's Soliloquy

Honorable Men

THE "ABSOLUTE FREEDOM" promulgated and practiced by some of our brash and vociferous minorities today should rather be termed absolute license: the prerogative to enjoy the rights of a democratic society without assuming the responsibilities that must morally complement those rights. Destructive criticism of our social order without the implementation of constructive alternatives constitutes nihilism: the demolition of institutions and values not only for the revolutionaries themselves but for the total society.

Individuals who coalesce into mobs are rarely responsible citizens—either singly or socially. Their mass ideology fosters the delusion that government must generously provide for its people instead of expecting them to provide for themselves: a fallacy that breeds militant intolerance and hostility toward others who neither share nor condone their ideology.

Of course we must listen and try to understand the minority malcontents our social system has unwittingly produced; we must encourage and educate individuals and groups to improve their economic status and elevate their social standards. But we need not identify with them or promote their ideologies. A healthy society encourages the symbiotic, not the parasitic role in its members.

Within some segments of our society a few of the finest terms in the English language are growing obsolete: personal integrity, self-reliance, social-mindedness, and nobility of spirit. Also becoming anachronistic is the word honor—about which Marlowe said:

"Honour is purchased by the deeds we do;
* * * honour is not won,
Until some honourable deed be done."

On very rare occasions there may have been minor violations of our ethical code of honor by some of us members of the medical profession, when we were young, over-articulate, idealistic, and perhaps a bit rebellious against authority and intolerant of institutionalization; nevertheless, we outgrew our crusaders complex and matured into the realization that we must share and thereby communalize our knowledge for the benefit of all—to the exclusion of none.

To expand our horizons and sharpen our perspective this issue of MINNESOTA MEDICINE, like some of the other Special Issues, is endeavoring to explore beyond the confines of our local society: to benefit from experience and instruction available from other sources.

The United States Air Force can be justly proud of its young members who have in this issue shared with us their research and achievement—each in his own vineyard. We can one and all profit from their valuable contributions.

We herewith salute these men, their dedication to their profession and their service to humanity. They are honorable men, indeed!

Carl O. Rice, M.D.

Old Doc Hess Says: If you endeavor to think in accordance with the mind of the masses instead of with your own excellent brain, your thoughts may originate from an inferior and unworthy source. COR

They serve God well, Who serve his creatures.—CAROLINE NORTON

Bygone Gout "Cures"

For the antiquarian interested in ancient and obsolete materia medica, literature provides some quaint and preposterous cures for age-old diseases afflicting man.*

The simplest and most disarmingly naive treatment for gout was that advocated and employed by Hippocrates in 300 B.C., which persisted for some 800 centuries thereafter: namely, the burning of flax adjacent to the gouty body area. Presumably the disease was allergic to flax smoke.

Apocryphal as it may now sound, the medical advice of Aetius of Mesopotamia about 500 A.D. consisted of the following 12-month program:

"In January: take a glass of pure wine every morning! February, eat not beets; March: mix sweets with eatables and drinkables; April: refrain from horse radish; May: eat no polypus fishes; June: take cold water every morning; July: abstain from venery; August: eat no mallows; September: drink only milk; October: garlic must be eaten; November: bathing is prohibited; December: eat freely of cabbage."

Around 550 A.D. Aetius' unique recommendation was superseded by Alexander of Tralles' repellent prescription of:

"A mixture of caraway seeds, anise, rhubarb, wolf's milk, vinegar, honey, dill, pepper, ginger, aloes, and—, pretty much by choice—colchicum."

In the seventeenth century a Dr. Daniel Sennart of Prussia proffered this bizarre combination:

"A poultice composed of marsh-mallow leaves, cabbage, barley, and frog sperm."

Also at the same time a Dr. John Loselous of Germany presented his gout patients with the following startling directions:

"Shave with a razor the hair off both legs, and at the same time cut the nails of hands and feet. This should be in the spring when sap is flowing, and the day before new moon. Make a hole right into the heartwood of a poplar or oak tree and insert the hair and nails. Stop it tight with a plug made of a branch of the tree, and the transplantation is perfect. Cut off close to the tree that part of plug that sticks out, and the next day plaster the place well with cow dung. If the patient does not in the next three months feel the *malum* again, he can credit it to the tree."

The year 1735 produced one mind-over-matter practitioner, Sir Richard Blackmore, who loftily and authoritatively asserted: "Fright can cause and cure an attack." Obviously, in his opinion gout was psychosomatic.

Of all the above fantastic specifics only one, colchicum, again saw the light after long eclipse. Its use was revived in 1763, reportedly by Baron von Strenck of Vienna, and was later introduced into the United States by Benjamin Franklin, himself a gout sufferer.

Ironically, colchicum was the one effective ingredient in Aetius' formula, but included as a purgative only, and later omitted, thereby markedly diminishing the efficacy of his prescription.

---

*Berton Roueche "Eleven Blue Men."

Marriages may be made in heaven, but man is responsible for the maintenance work.—Changing Times

What counts in knowledge is that which you learn after you reach the point where you know it all.—Advertiser's Digest

Curbstone Consultation

Burns

QUESTION: What is the current status of the topical treatment of burns?

ANSWER: At the present time there are five compounds that appear promising in the control of surface infection in burns. Two of these, 0.5% Silver Nitrate Solution and Gentamycin are commercially available; Mafenide or Sulfamylon is expected to be released at any time; and 0.5% Silver Acetate Cream and Silver Sulfadiazine (CF-100) Ointment are still investigational drugs.

Since the advent of 0.5% Silver Nitrate Solution as advocated by Moyer,[5] many reports have shown control of surface bacteria and progressive epithelialization. However, problems with linen staining, the need to keep dressings continuously wet, chloride depletion, and methemoglobinemia[8] have detracted from its usefulness.

Gentamycin, as advocated by Stone, has shown good control of surface bacteria, especially Pseudomonas, and does not appear to interfere with epithelialization. Ototoxicity and nephrotoxicity have been reported as side effects.[6]

Sulfamylon, as advocated by Moncrief and the Brooke Army Hospital group,[4] has prevented Pseudomonas colonization while not interfering with epithelialization. Problems with carbonic anhydrase inhibition, acidosis, pain on application and, recently, a report by Burke et al. concerning the development of hyaline membrane disease in guinea pigs[3] treated with Sulfamylon have encouraged investigators to search for better agents.

Two new compounds have recently been reported. Butcher et al. in St. Louis have been using a 0.5% Silver Acetate Cream which appears to give fewer problems with chloride depletion, linen staining, and methemoglobinemia; but only a few patients have been so treated.[1] The action is similar to Silver Nitrate Solution.

The other new compound as reported by Fox and Stanford is Silver Sulfadiazine or CF-100.[2,7] Its use in over 280 patients has shown elimination of Pseudomonas on surface cultures and no interference with wound healing. There is no pain on application, no staining of linens and no carbonic anhydrase or electrolyte problems. Application of this insoluble compound is by gloved hand one time per day after washing. Radioactive silver studies have shown the silver to combine with the DNA of sulfhydryl groups of the bacteria; hence one receives the bactericidal effects of silver combined with the bacteriostatic effect of sulfadiazine. As such, the drug is lethal to many organisms, especially Pseudomonas. Early clinical trials look extremely promising.

William Stanford, Lt. Colonel, USAF, MC
Assistant Chief, Thoracic Surgery Service

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Breast Mass after Mastectomy

QUESTION: What do I do with an anterior chest mass in a patient who has had a bilateral subcutaneous mastectomy and breast implant reconstruction?

ANSWER: Treat the mass as any other dominant breast mass. After no longer than one to two months of observation, do an excisional biopsy for small or medium size masses, or an incisional biopsy for larger masses. Even though a subcutaneous near total mastectomy has been performed to prevent carcinoma, existing breast may remain unless the nipple is removed and unless all subcutaneous tissue and fascia are removed, (1) superiorly to the clavicles, (2) medially to past the midline of the chest, (3) inferiorly well below the costal margin onto the rectus abdominus muscle, (4) laterally past the border of the latissimus dorsi, and (5) well into the axilla to remove the tail of the breast.

Residual tissue can develop carcinoma just as any other breast tissue can. There is no evidence to even suggest that silastic implant material has caused cancer, and in the two cases in our series the cancer was medial to the implant and not in contact with the silastic or its dacron mesh. Subcutaneous mastectomy and silastic implant reconstruction constitute a very good prophylactic procedure in certain clinical situations, a common example being the patient with numerous cysts and breast masses and numerous previous biopsies, with the expectation of numerous future biopsies. Even though less than 100% of breast parenchyma is removed, more than 99% is removed; therefore 99% of the cancer-developing tissue is eliminated. The remaining tissue, if it develops carcinoma, is relatively easy to examine, and if it is realized that cancer can still develop in this situation, small early lesions can be discovered and treated early.

If the lesion is not cancer, a meticulous two or three-layer closure under strict aseptic operating room technique is necessary to prevent infection and/or rejection of the implant.

The cancer surgery itself requires removal of the pectoral muscles since some of the breast implants are placed beneath the pectoral muscles, sometimes intentionally and sometimes accidentally. When the pectorals are removed, most surgeons will elect to perform the axillary dissection and complete the standard radical mastectomy. If any bilateral breast surgery has been performed in the previous two to five years, bilateral breast cancer cell seeding may have occurred and bilateral breast cancer surgery is required.

It may be that a bilateral mastectomy is required in all cases, regardless of the time interval. The initial subcutaneous mastectomy and implant reconstruction are usually performed after several previous breast biopsies; and, in that instance, we recommend a four to eight-centimeter normal tissue margin removal of skin scars with the mastectomy specimen. One of our patients had her cancer develop in a scar through which three previous biopsies had been performed over a six-year period. Skin grafts will be necessary when such wide skin removal is required.

David G. Bowers, Jr., Lt. Colonel, USAF, MC
Chief, Plastic Surgery Service

Spontaneous Pneumothorax

QUESTION: Is a chest tube necessary in the management of spontaneous pneumothorax?

ANSWER: Yes, The principle to be followed in the treatment of pneumothorax is full expansion of the lung with obliteration of any pleural air space. Insertion of a large-bore intercostal catheter seems to be the most expeditious method of accomplishing this with very little morbidity. Prolonged periods of bedrest waiting for a collapsed lung to re-expand are not only risky to the patient but can result in prolonged hospitalization with no assurance that a chest tube will not be necessary at a later date.

Thoracentesis is not always satisfactory because it may require multiple taps and the patient is left with the possibility of recurrence of a pneumothorax. Small-bore tubes or "intra-caths" likewise are not satisfactory because they may become sealed off; and they produce no intrapleural reaction that may help prevent future pneumothoraces.

I recommend insertion of a (30-36 French) rubber catheter in the 2nd anterior interspace, and connection of the catheter to an underwater seal trap with suction applied to the system. The tube is removed 24 hours after all air leaks have stopped and the lung has fully expanded. If the air leak persists for seven days or full lung expansion cannot be achieved, then open thoracotomy with suture of the bronchial leak and decortication, if necessary, should be accomplished.

Bryon N. Dooley, Lt. Colonel, USAF, MC
Chief, Thoracic Surgery Service

God made everything out of nothing. But the nothingness shows through.—Paul Valery

Some men are born great, some achieve greatness, and others just keep still. —Kin Hubbard

Teach thy tongue to say, "I do not know."—Talmud

The Fortunate One.

Her urinary tract infection reveals itself through pain and discomfort.

While the pain and discomfort of a G.U. infection are anything but pleasant, the patient may be luckier than she realizes. That burning sensation (and/or frequency, urgency, dysuria) is a usually reliable sign of a urinary tract infection. And it's her good fortune that her infection won't go undetected...or untreated.

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Indications: Urinary tract infections with associated pain or discomfort when due to susceptible organisms; prophylactically in urologic surgery, catheterization and instrumentation.

Contraindicated in sulfonamide-sensitive patients, pregnant females at term, premature infants, newborn infants during the first three months of life, glomerular nephritis, severe hepatitis, uremia and pyelonephritis of pregnancy with gastrointestinal disturbances.

Warnings: Use only after critical appraisal in patients with liver damage, renal damage, urinary obstruction or blood dyscrasias. If toxic or hypersensitivity reactions or blood dyscrasias occur, discontinue therapy. In closely intermittent or prolonged therapy, blood counts and liver and kidney function tests should be performed.

Precautions: Observe usual sulfonamide therapy precautions including maintenance of an adequate fluid intake. Use with caution in patients with histories of allergies and/or asthma. Patients with impaired renal function should be followed closely since renal impairment may cause excessive drug accumulation. Occasional failures may occur due to resistant microorganisms. Not effective in virus and rickettsial infections.

Adverse Reactions: Headache, nausea, vomiting, urticaria, diarrhea, hepatitis, pancreatitis, blood dyscrasias, neuropathy, drug fever, skin rash, Stevens-Johnson syndrome, injection of the conjunctiva and sclera, petechiae, purpura, hematuria or crystalluria may occur, in which case the dosage should be decreased or the drug withdrawn.

Dosage: Adults—4 tablets initially, then 2 tablets morning and evening.

How Supplied: Tablets, bottles of 50.

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Bad Health and Big Shots

Ill health is supposedly much pleasanter nowadays than it was in the past but, as far as I can see, people of all epochs have had little trouble putting up with it. Some months ago when I was re-fighting the War Between the States, assisted by Douglas Southall Freeman and Carl Sandburg, I asked myself over and over again how men whose health was at best indifferent could play such important roles in this titanic struggle. Of the Union administrative big shots, Honest Abe alone seemed to have a physique commensurate with the demands made upon it. Stanton was dyspeptic as an over-age sow and Seward was very delicate. At the start of the war, General Winfield Scott ran the Union Army from a sofa.

Ill health was just as prevalent among the Confederates. Jeff Davis was pure courage and passion prodding along a semi-invalid body. Alexander Stephens was one of the frailest statesmen that ever lived. General Lee was by no means an invalid, but his heart was in perilous condition before the war was half over. Stonewall Jackson couldn't function unless he had loads of sleep. Dick Ewell was lame and liverish and D. H. Hill had numerous afflictions. The list is endless.

But all these creaky people were in the pink of condition compared to some of the dillies of the more distant past. Naturally, the opinions of modern doctors as to what ailed a big shot centuries ago must be taken with a certain reserve, inasmuch as they often err in their diagnosis of contemporary specimens. Furthermore, devotees of each branch of the profession consider it a point of honor to fasten the disease that interests them most on as many celebrities as possible. Thus, poor old King James I is proudly portrayed by competing specialists as suffering from catarrh, gluttony, adenoids, tonsils, jaundice, diarrhea, septic teeth, arthritis, Bright's disease, piles, ulcers, and six kinds of heart trouble. Perhaps he did so suffer. If he did, he neatly typified for fifty-five years in his own royal person the variegated misery of all mankind.*

***Sprague, Marshall**: The Business of Getting Well, 1943.

Fraud in the Mails

In 1913 the Post Office Department decided to check into Interstate's* methods of operation. A new political administration was in office, and postal attorneys may not have known about Hayes' earlier efforts at conspicuous rectitude. . . . At any rate postal inspectors, following their usual procedure, began to write Interstate heartrending letters.

"There is something wrong with my testicles," one test letter began, "and I don't know what to make of it. I noticed for some time that they don't hang even and that the left one hangs lower. I ain't got the nerve to ask our doctor about it so am writing to you to find out what you think about it. Please use plain envelope."

Of course, this perfectly natural condition was, to Interstate, an ailment. You have "swollen testicles," the company answered, and need Man Medicine for "quick recovery."†

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*Interstate was a mail-order company that advertised and sold Man Medicine.

†James Harvey Young: The Medical Messiahs, 1967.

The Viewing Box

Nephrocalcinosis

A 32-YEAR-OLD WOMAN was admitted to Wilford Hall USAF Hospital for evaluation of recurrent pyelonephritis. The patient had initially developed a renal infection during her first pregnancy 16 years previously. Since that time she had had many recurrences which were treated with a number of different urinary tract antibiotics. During the four years prior to admission she was almost completely symptom-free. Approximately six years before admission she was first noted to have renal calcifications. Both of the patient's parents had passed renal stones. She denied any personal or family history of tuberculosis.

The admission physical examination was unremarkable except for minimal bilateral costovertebral angle tenderness. A few red and white blood cells were seen on urinalysis. Serum electrolytes, calcium, phosphorus, and uric acid were normal. Urinary excretion of calcium and phosphorus was also normal.

A supine abdominal film (Figure 1) demonstrated multiple calcifications

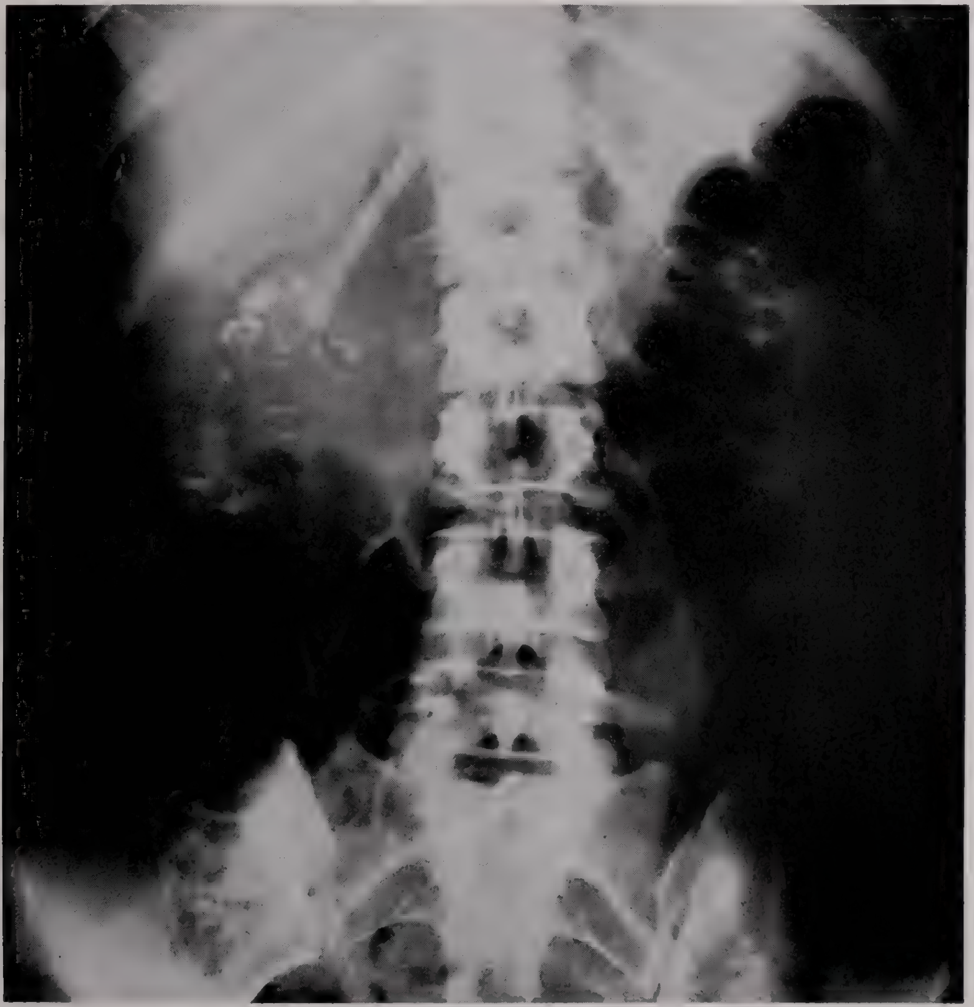

Figure 1

in the renal parenchyma bilaterally, which appeared to be in the area of the pyramids. The kidneys were normal in size and functioned well bilaterally on an intravenous urogram (Figure 2). There were many extracalyceal collections in the pyramids of the right kidney (Figure 3), most of them appearing to radiate out from the calyces.

The patient was readmitted on several subsequent occasions because of urinary tract calculi. One of these was analyzed and contained calcium and magnesium phosphates.

What is your diagnosis?

Diagnosis: Medullary Sponge Kidney.

In addition to medullary sponge kidney, the differential diagnosis of nephrocalcinosis is an extensive one. In this patient, however, those entities accompanied by hypercalcemia or hypercalciuria could be eliminated. These include primary and secondary hyperparathyroidism, sarcoidosis, hypercalcemia associated with malignancies, the calcium mobilization occurring with prolonged bed rest, milk-alkali syndrome, vitamin D intoxication, and idiopathic hypercalciuria. In addition, the serum and urinary findings permit exclusion of renal tubular acidosis, with or without amino-aciduria. The absence of oxalate in the analyzed stone makes oxalosis an extremely unlikely diagnosis. Finally, there is no radiographic evidence that infection, either tuberculous or pyogenic, represents the underlying etiology.

Medullary sponge kidney, or renal tubular ectasia, is a developmental abnormality in which there is dilatation of the renal tubules within the pyramids, with small diverticula or cysts arising from these tubules. On cut section these pyramids have the appearance of sponges. Disagreement exists as to the etiology of the lesion. One view is that back-pressure secondary to obstruction causes the tubular dilatation. A second view is that it is part of the spectrum of polycystic disease, since the two processes have been found in the same families and, in fact, in the same patient.

The clinical presentation of patients with medullary sponge kidneys is generally due to complications of this disease, as in this patient. Frequent infections and stone formation may lead to compromise of renal function; however, many never suffer any ill effects referable to this process. Renal

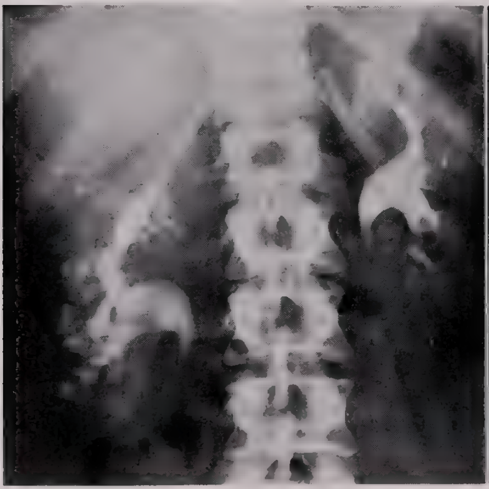

Figure 2

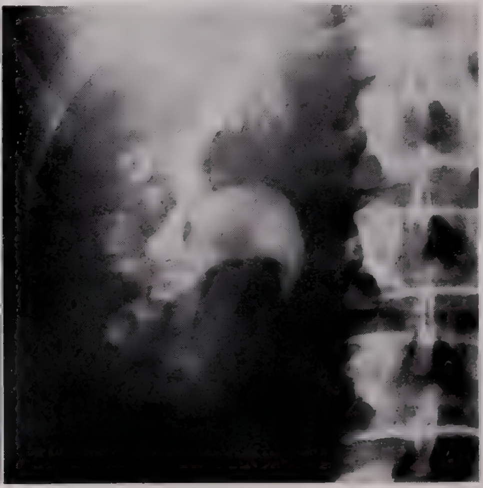

Figure 3

calcifications may be an unsuspected finding on an abdominal film.

Radiographically there is nephrocalcinosis which is generally bilateral, but not necessarily symmetric. Renal or ureteral stones may be present. A urogram may demonstrate dilated tubules radiating out from the calyces into the pyramids. In addition, small rounded collections of contrast material may be seen in the pyramids representing small cysts. When the changes of chronic pyelonephritis are superimposed, it may be impossible to determine the underlying process.

Richard A. Rosen, Captain, USAF, MC*

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*From the Department of Radiology, Wilford Hall USAF Hospital, Lackland Air Force Base, Texas.

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Medieval Science

In considering medieval science we cannot fail to be struck by two peculiarities, the solidarity and interdependence of all its branches, and the dominance of certain numbers in its basic conceptions. . . . It is seldom that we find a medieval physician content to confine his attention exclusively to the medical sciences, or unwilling to include in his studies astronomy and astrology, music and mathematics, and even ethics, metaphysics and politics.

The strange sect of the Ismailis or Esoterics instructed their missionaries to arouse the curiosity of the potential proselyte by such questions as "Why has a man seven cervical and twelve dorsal vertebrae?" "Why has each of the fingers three joints but the thumb only two?" and the like; and it was to them a fact of infinite significance that the number of joints on the two hands agreed with the number of permanent teeth, the number of days of the lunar month, and the number of letters in the Arabic alphabet. So in their cosmogony we notice the great part played by the numbers four, seven and twelve. Thus we have the four Natural Properties, Heat, Cold, Dryness and Moisture; the four Seasons; the four Humors, the four Winds, and the like. Also the seven Planets, the seven Climes, the seven Days of the Week, and the Seven Seas; the twelve Signs of the Zodiac, the twelve Months of the Year, and so on.*

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*Edward G. Browne: Arabian Medicine, 1921.

I want to be thoroughly used before I die, and I want to die gloriously solvent, intellectually, morally, and financially.—George Bernard Shaw

When the defects of others are perceived with so much clarity, it is because one possesses them oneself.—Jules Renard

FEATURE SPECIAL

Minnesota State Board of Medical Examiners

Notice of Hearing

Notice is hereby given that a public hearing will be held pursuant to M.S. 1967, Section 15.0412, Subdivision 4, in the above entitled matter, in the office of Minnesota State Board of Medical Examiners, 496 Lowry Medical Arts Building, Saint Paul, Minnesota, on April 19, 1969, commencing at 10:30 a.m. and continuing until all representatives of associations or other interested groups or persons have had an opportunity to be heard concerning adoption of the proposed amendments to the rules captioned above by submitting either oral or written data, statements, or arguments. Statements or briefs may be submitted without appearing at the hearing.

The proposed amendments to rules are:

I. Proposed amendment to Rule ME 4(b)(4).

Rule ME 4(b)(4) is hereby amended by adding thereto the following sentence. "Such evidence shall not be required, however, if the applicant: (a) was licensed by examination in a state which at the time of applicant's licensure therein did not require that he had been awarded a Certificate by The Educational Council for Foreign Medical Graduates, or (b) is a diplomate of a medical specialty board approved by the American Medical Association."

II. Proposed amendment to Rule ME 5(b)(3).

Rule ME 5(b)(3) is hereby amended by adding thereto the following sentence. "The evidence required in clause (a) hereof shall not be required, however, if the applicant is a diplomate of a medical specialty board approved by the American Medical Association."

III. Proposed amendment to Rule ME 7(a)(8).

Rule ME 7(a)(8) is hereby amended by adding thereto the following sentence. "The evidence required in clause (a) hereof shall not be required, however, if the applicant is a diplomate of a medical specialty board approved by the American Medical Association."

Minnesota State Board of Medical Examiners
J. P. Medelman, M.D.
Secretary-Treasurer

President's Letter (continued from page 387)

> "The surgeon should be learned, skilled, ingenious, and of good morals. Be bold in things that are sane, cautious in dangers; avoid evil cures and practices; be gracious to the sick, obliging to his colleagues wise in his predictions. Be chaste, sober, pitiful, and merciful; not covetous nor extortionate of money; but let the recompense be moderate, according to the work, the means of the sick, the character of the issue or event, and its dignity."

In his introduction to "The Apologie and Treatise of Ambroise Paré" Geoffrey Keynes notes, "There is no more potent stimulus to advance in surgery than the exigencies of war." Our military services which have known such men as Walter Reed, have made increasingly valuable contributions to the field of medicine, especially since World War II. Our guests from the United States Air Force exemplify this high level of achievement. Himself a veteran of the Medical Corps of the United States Navy (World War II), the undersigned takes particular pride in welcoming these colleagues from the Wilford Hall USAF Hospital.

O. L. N. Nelson, M.D.,
President
Minnesota State Medical Association

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for unearthly cough

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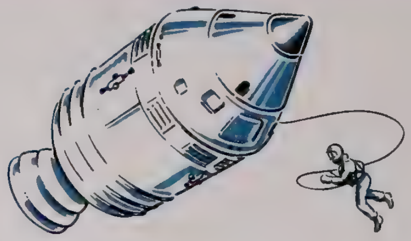

Man in space, now fait accompli, re-emphasizes the importance of Uro-Phosphate therapy. Research into the effect of space travel on the astronaut reveals that weightlessness causes loss of bone calcium. As the bones are required to bear less and less of the weight of the body they lose calcium, increasing the calcium content of the urine. When physical activity is reduced, the acidity of the urine should be adjusted to keep increased calcium in solution . . . . a prophylaxis to prevent kidney or bladder calculi.

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Uro-Phosphate is safe for continuous use. There are no contra-indications other than acidosis. It can be given in sufficient amount to keep the urine clear, acid and sterile. A heavy sugar coating protects its potency.

Dosage:

For protection of the inactive patient 1 or 2 tablets every 4 to 6 hours is usually sufficient to keep the urine clear, acid and sterile.

2 tablets on retiring will keep residual urine acid and sterile, contributing to comfort and rest.

A clinical supply will be sent to physicians and hospitals on request.

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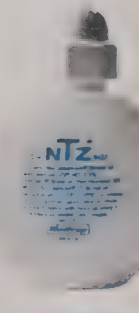

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ANTISECRETORY SEDATIVE

Dermatology

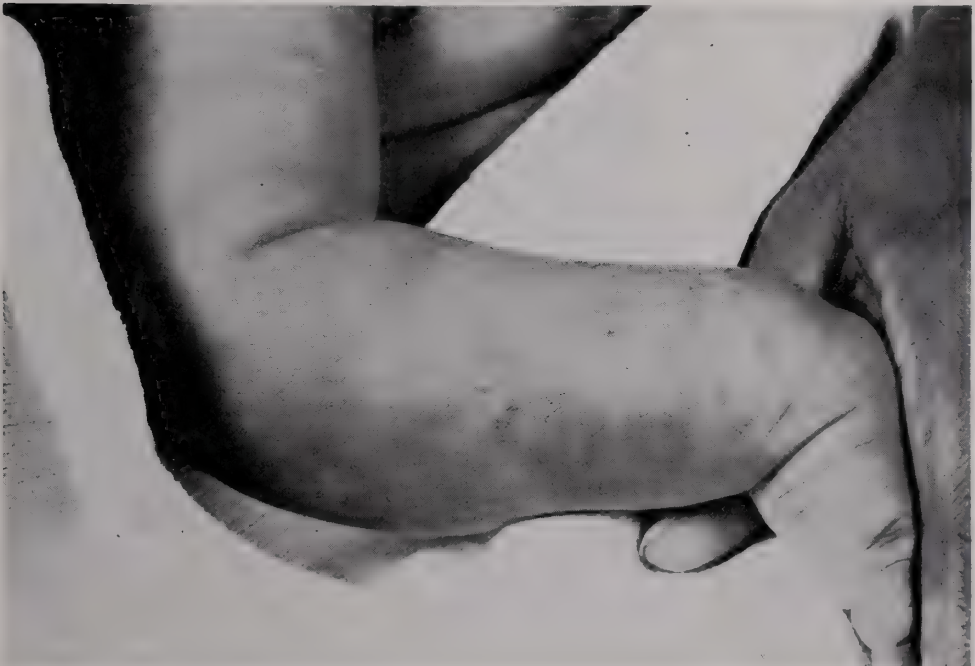
Systemic Lupus Erythematosus in the Newborn

THE OCCURRENCE OF SYSTEMIC LUPUS erythematosus in a new-born infant is a distinct rarity. Several authors[1-4] reported skin changes consistent with this uncommon entity. Jackson[5] reported that discoid lupus erythematosus was produced in an infant in placental transmission of the lupus erythematosus cell factor from the mother who had systemic lupus erythematosus. McCuistion and Schoch[4] also had a unique case involving a newborn with discoid lupus erythematosus; the mother had acute disseminated lupus erythematosus 11 months post partum.

The present report concerns a newborn infant who demonstrated clinically all of the characteristic features of disseminated discoid lupus erythematosus at birth.

Case Report

A negro infant girl, born December 26, 1967, was the product of a full-term pregnancy which was complicated only by a urinary tract infection. She was noted to have a dusky erythematous, depressed and atrophic eruption over the malar eminences and forehead. The referring physician reported that these sharply demarcated, irregular patches were present at birth. During the three months following birth, the lesions became more scattered until they included the frontal hairline and forehead, cheeks, chin, chest, arms and back. The original areas on the cheeks became confluent, and follicular plugging and scale formation was particularly evident in these patches. The skin lesions (Figure) were unresponsive to hydrocortisone cream



Figure—Clinically obvious lesions of lupus erythematosus at age three months.

during the first few months, and new skin lesions continued to appear well into the fourth month.

The infant developed well from a birth weight of seven pounds, two ounces and remained in the 90th percentile for weight and the 75th percentile for height. A systolic heart murmur discovered at one month was diagnosed as possible tetralogy of Fallot, although a pulmonic valvular stenosis could not be ruled out definitely.

Skin biopsy was performed March 27, 1968, and a supravital bone marrow on the same date revealed typical lupus erythematosus cells; therefore the diagnosis was changed from the initial impression of disseminated discoid lupus erythematosus to systemic lupus erythematosus. The lupus erythematosus cell test was negative in the peripheral blood. The antinuclear antibody titer was 1:10. The white blood count was 7,800 with 23 percent neutrophils and 71 percent lymphocytes. The sedimentation rate was 2 mm/hr, the hemoglobin 10.8 gm/100 ml, and the hematocrit 33 percent. Urinalysis was normal. Latex globulin slide agglutination for rheumatoid arthritis was negative. VDRL was nonreactive. Blood urea nitrogen was 15 mg/100 ml, and serum protein electrophoresis was within normal limits.

Both parents received laboratory tests including the serologic test for syphilis, lupus erythematosus preparations (peripheral blood), and latex fixation. All of these tests were normal. No physical abnormality or significant familial historical finding could be elicited from the parents.

Comment

The familial incidence of lupus erythematosus is well documented. Rona[6] and Sequeira[7] presented siblings with the disease at the turn of the century, and many authors[8-12] have reported familial lupus erythematosus since that time.

Bridge and Foley[13] demonstrated that transplacental passage of the lupus erythematosus factor did occur. They identified lupus erythematosus cells in the mother, in the cord blood, and in the bone marrow of the normal infant. The lupus erythematosus cell phenomenon disappeared when the infant was four months of age. Beck,[14] in an excellent study, identified antinuclear antibody (7S globulin) in the sera of infants at birth in titers similar to those in the maternal sera of three mothers who had systemic lupus erythematosus. However, evidence of lupus erythematosus did not develop in the infants.

It is difficult to investigate the sequence of events necessary for the actual development of typical lupus erythematosus lesions in the newborn. The problems of lowered fertility[15] and high fetal mortality[16] in systemic lupus erythematosus allow few opportunities for a study of the effects of passively transferred auto-antibodies in infants born to affected mothers. Therefore the exact mechanism for transfer of this ancient skin and systemic disease from an affected mother to her infant remains a mystery. It is even more difficult to understand how an apparently normal and unaffected couple can become the parents of a newborn with obvious lupus erythematosus lesions.

Summary

A newborn infant with clinically obvious lesions of lupus erythematosus has been described. A bone marrow supravital stain revealed typical lupus erythematosus cells. The skin lesions increased in number and continued to spread to previously uninvolved sites, even into the fourth month. The parents had no physical or laboratory changes suggestive of lupus erythematosus, and there was no family history of the disease.

William R. East, Major, USAF, MC*
Lee R. Lumpkin, Colonel, USAF, MC*

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*From the Dermatology Service, Department of Medicine, Wilford Hall USAF Hospital, Aerospace Medical Division (AFSC), Lackland Air Force Base, Texas.

References may be secured from the author or the reprints.

Fracture Conference

Fracture Dislocation of the Proximal Radial Epiphysis

A nine-year-old male fell from a tree 30 minutes prior to being seen at the emergency room of Wilford Hall USAF Hospital. He claimed that he fell on his hands with both arms straight. He had severe pain and swelling of the right wrist, associated with moderate pain of the left elbow and resistance to any movement of the left forearm. The neurovascular status of both hands was intact.

X-rays showed a fracture of the distal right radius with volar displacement (Figures 1 and

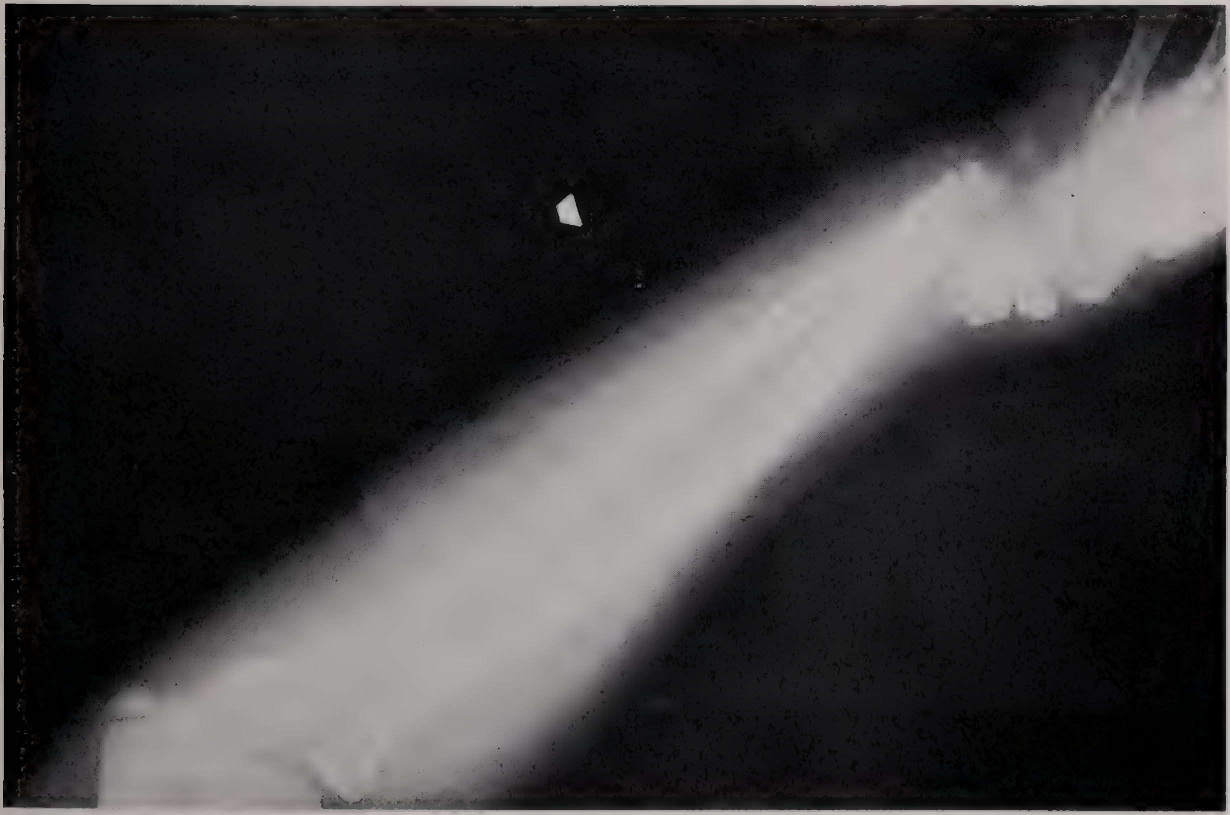

Fig. 1—Displaced fracture of the right radius; anteroposterior view.

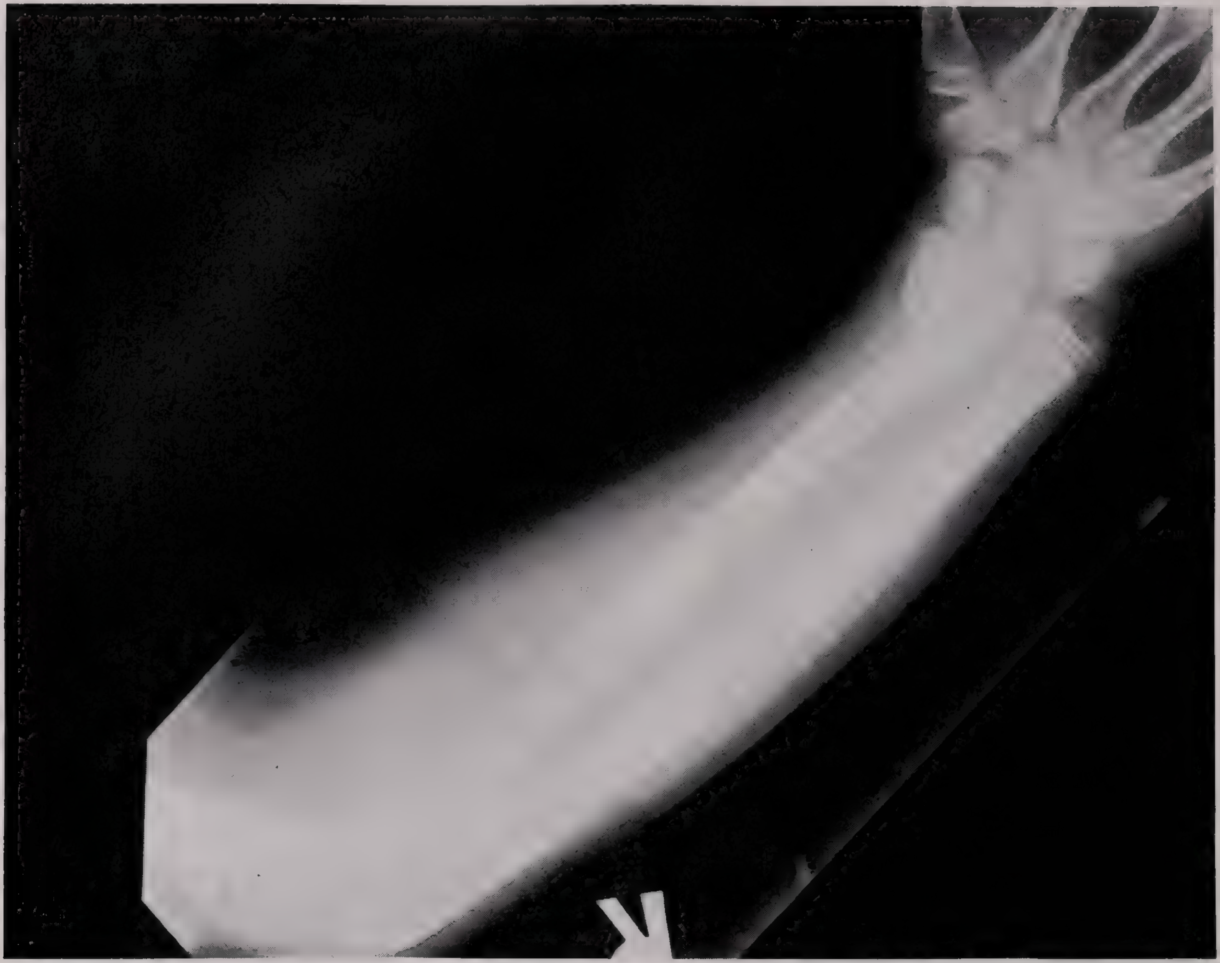

Fig. 2—Displaced fracture of the right radius; lateral view.

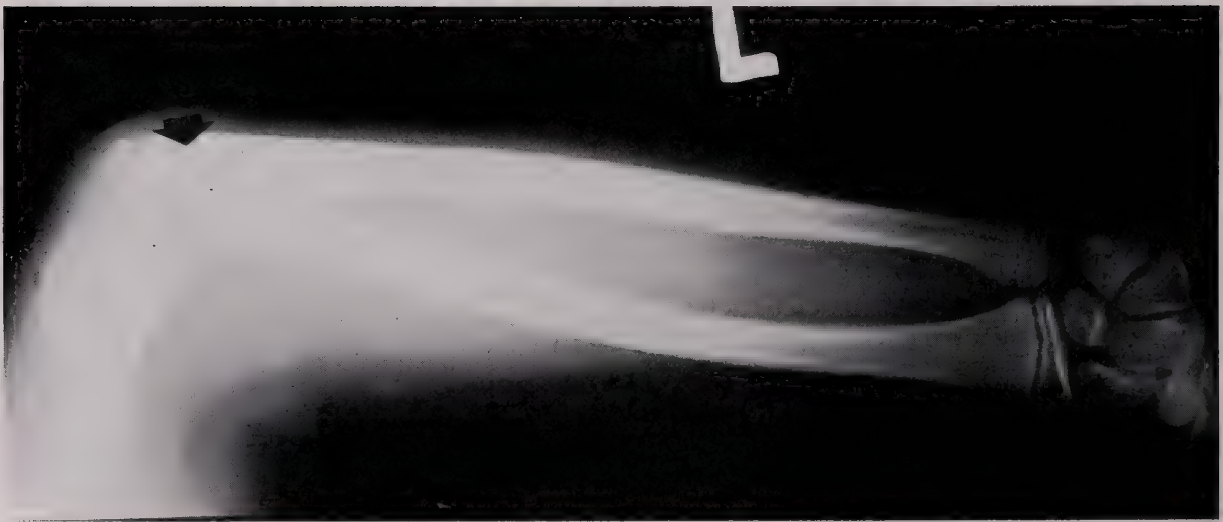

Fig. 3— Fracture-dislocation of the proximal epiphysis of the left radius.

2), also a fracture of the left radial head, with lateral displacement of more than 60 degrees (Figure 3).

The patient was taken to the operating room and, under general anesthesia, a closed reduction of the fracture-dislocation of the radial head was attempted. However, the angulation of the proximal radial epiphysis, as determined on the anteroposterior x-ray, was not improved. An incision was made over the lateral epicondyle of the humerus curving distally over the proximal 4 cm of the ulna. After the subcutaneous tissues and fascia had been split in the line of the incision, the interval between the anconeus and extensor carpi ulnaris muscles was developed. Then the radial head was found with the articular surface pointing laterally and slightly distally, completely out of contact with the remainder of the radius.

A buttonhole-shaped rent was seen in the orbicular ligament. The radial head, or the proximal radial epiphysis, was manipulated toward the rent. With digital pressure on the proximal radial head and with the forearm adducted, the proximal radial epiphysis slipped through the rent and into normal alignment (Figure 4). The fracture was stable during supination and pronation, both in flexion and in extension. After closure of the wound, anterior and posterior splints were applied. The fracture of the distal right radius was reduced by

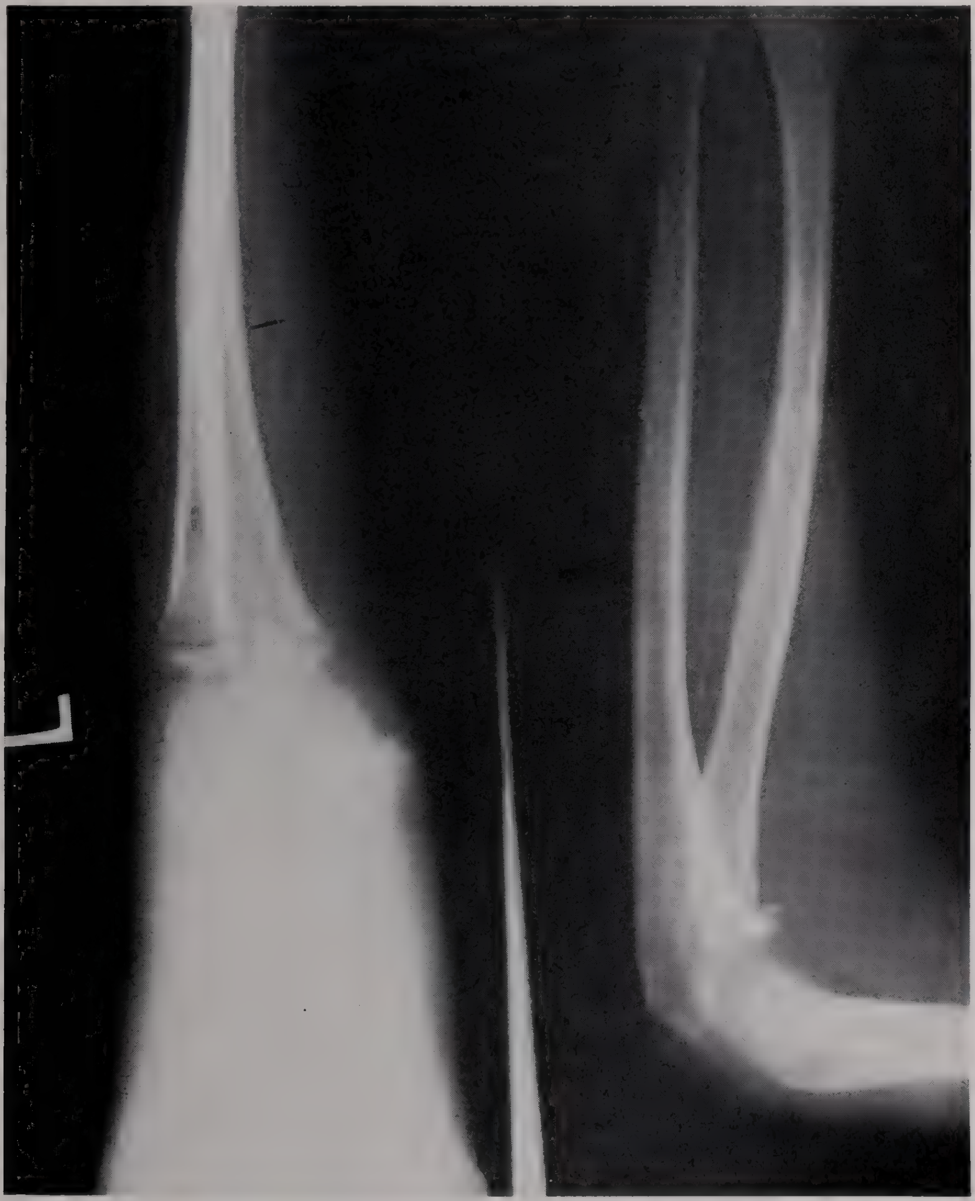

Fig. 4—X-ray following open reduction of fracture-dislocation of proximal radial epiphysis.

closed manipulation, and anterior and posterior splints were applied (Figure 5).

External immobilization of the left elbow was discontinued at three weeks (Figure 6). Gentle active motion was started, and the patient had a full range of motion at two months.

Discussion

Fracture-dislocation of the proximal radial epiphysis is a relatively rare injury seen in children between five and 14 years of age. The mechanism of injury is a fall on the hand with the forearm supinated and the elbow fully extended. With the elbow in extension, the slight valgus of the carrying angle directs the distal force toward the radiohumeral joint, and displacement of the proximal radial epiphysis results.

Removal of the radial head is a disastrous form of treatment in children,[1] for 25 percent of the growth in length of the radius occurs at the proximal radial epiphysis. Hence, removal may cause not only cubitus valgus at the elbow, but also radial deviation of the hand as a result of continued normal growth of the ulna.

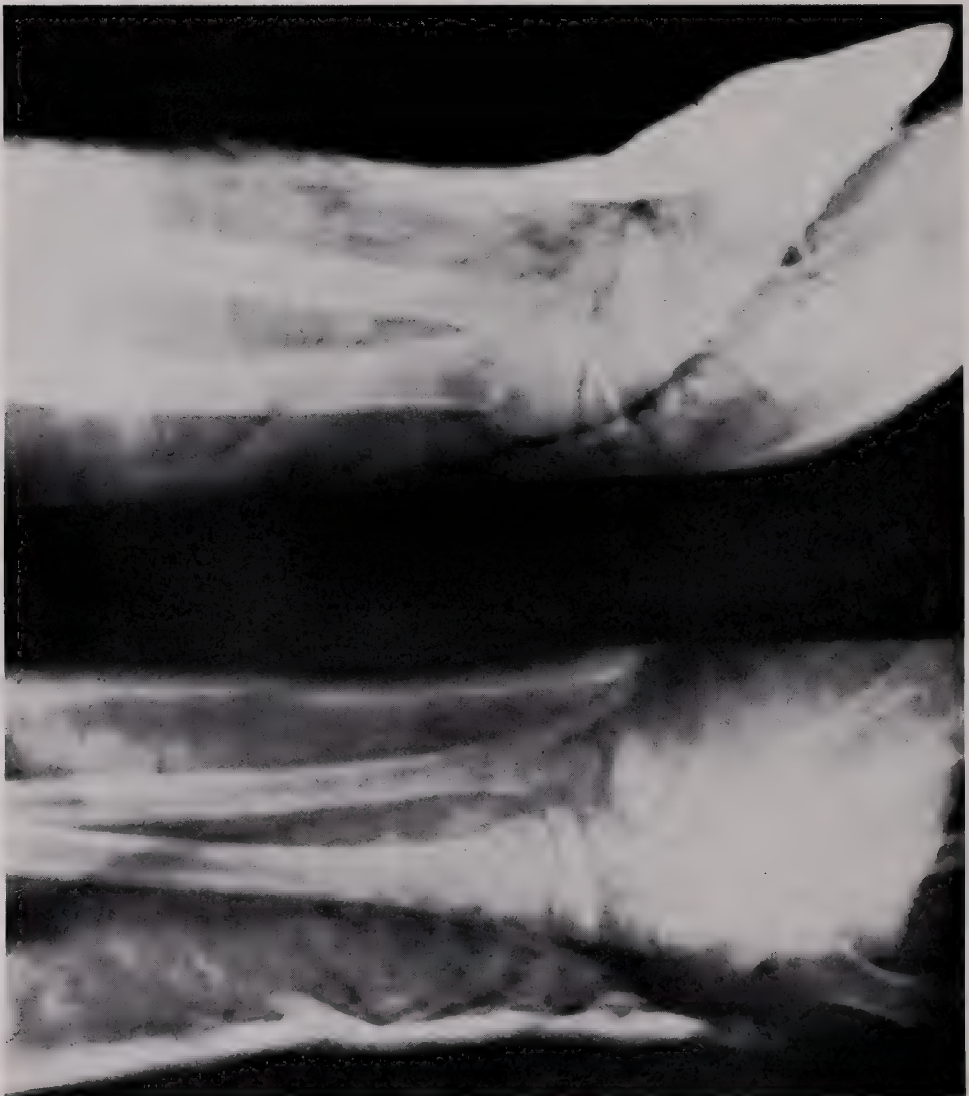

Fig. 5—Post-reduction x-ray of fracture of right distal radius.

The extent of the angular or rotational displacement of the proximal radial epiphysis, as seen on the anteroposterior x-ray of the elbow, determines the treatment. No reduction is needed for angulation from 0 to 30 degrees. A good result can be expected from immobilization for 21 days and then active exercises. When the angulation is from 30 to 60 degrees, a closed reduction should be attempted. Digital pressure is applied over the proximal radial epiphysis with the forearm adducted and simultaneous moderate supination and pronation of the forearm. According to Blount,[1] closed reduction is quite effective for an angulation of less than 45 degrees.

If closed reduction cannot bring the angulation down to less than 45 degrees, an open reduction should be done through the posterolateral approach to the radial head. For angulation of more than 60 degrees, closed reduction should be attempted, even though a satisfactory reduction is not likely. Repeated attempts at closed reduction should be resisted, for they can damage the epiphysis or destroy the orbicular ligament. Gentle open reduction of the proximal radial epiphysis should then be done. If the fracture is unstable after reduction, a small Kirschner wire can be used, but it must be

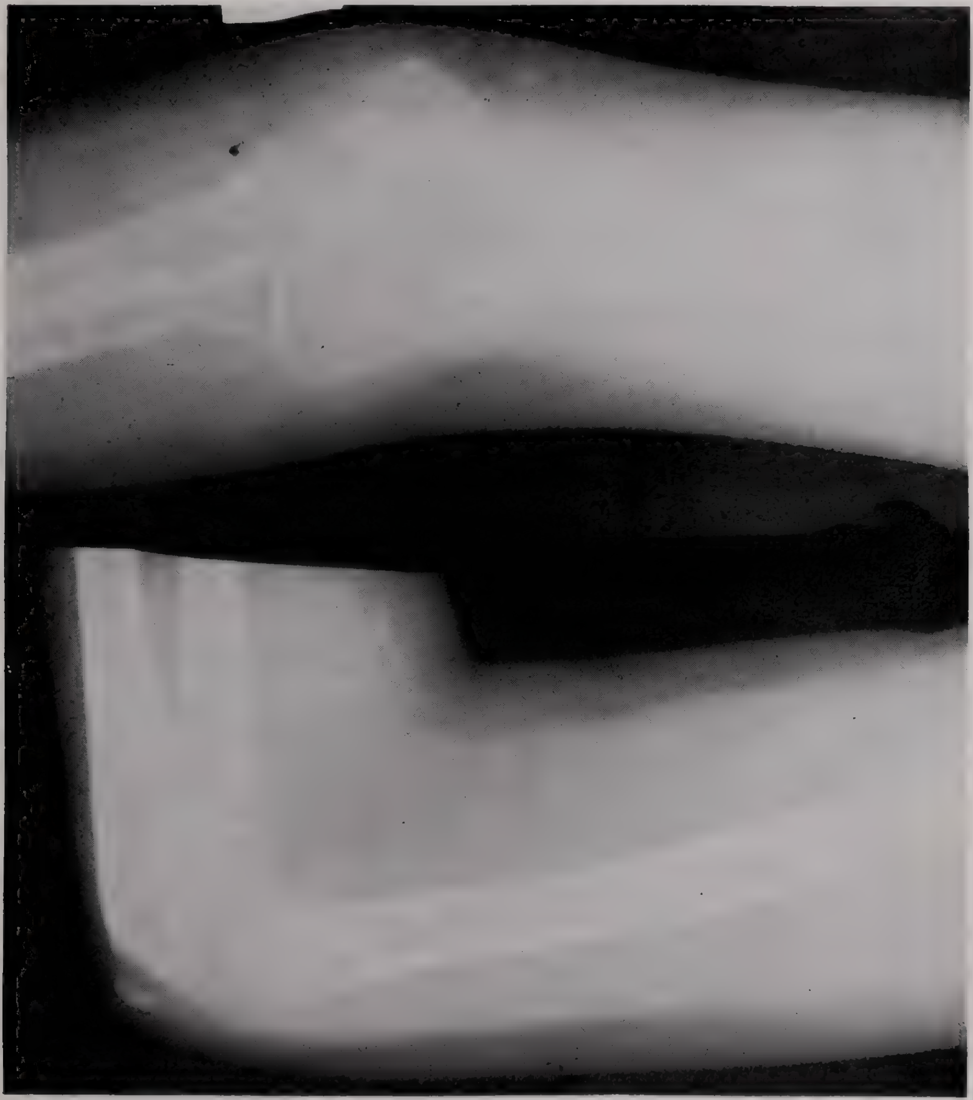

Fig. 6—X-ray taken three weeks post reduction of the proximal left radial epiphysis.

placed through the capitellum and the center of the proximal radial epiphysis.[2] Unless these requirements are met, damage to the epiphysis and premature closure are likely to occur. The Kirschner wire should be removed at three weeks and gentle active motion should be started.

Some authors believe that reduction will result in some limitation of motion when the final angulation exceeds 20 degrees.[3-5] Blount concedes this, but there is only slight limitation of supination with angulation of less than 45 degrees and usually the patient is not aware of this limitation.[1]

If the fracture is more than three weeks old, open reduction should not be performed, regardless of the rotational deformity,[1] because of the risk of radio-ulnar synostosis and severe limitation of motion.[2] The deformity should be left alone, and the radial head removed at skeletal maturity only if necessary.

Adequate treatment of the fracture depends upon recognition of the angular deformity on the anteroposterior x-ray of the elbow. Awareness of the fracture may depend upon the practice of obtaining x-rays of both ends of a fractured bone.

John F. Payne, Major, USAF, MC*
Jack L. Earle, Lt. Colonel, USAF, MC*

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*From the Department of Orthopaedic Surgery, Wilford Hall USAF Hospital, Lackland Air Force Base, Texas.

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Cowboy Doctors Made Mileage

Trying to care for the sick and hurt scattered over immense regions, cowboy doctors racked up cross-country riding records that rivaled those of the Pony Express. Dr. J. E. Hodge, Slim Buttes, the Dakotas, regularly rode 50 to 60 miles to the bedside of a patient. Dr. Urling C. Coe was accustomed to covering 80 miles of Oregon bunch grass country in a day; he clipped off 35 miles in three and a half hours over rough trails. When the Christmas tree caught fire in a hall crowded with ranch families at Silver Lake, Oregon, scores were fearfully burned. Dr. Bernard Daly rode 100 miles through the snow from Lakeview to find 38 victims already dead. He treated 36 and saved all but five with the assistance of cowboy nurses. Another Oregon doctor, F. C. Harley, Canyon City, rode so fast over primitive roads that he had to carry his hat in his hand to keep it from blowing away. Once he made a horseback call 250 miles away in Winnemucca, Nevada, and probably established the long-distance record for a cowboy doctor riding to his patient.*

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*Richard Dunlop: Doctors of the American Frontier, 1965.

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CONTRAINDICATIONS: Patients with glaucoma; prostatic hypertrophy and benign bladder neck obstruction; known hypersensitivity to chlordiazepoxide HCl and/or clidinium bromide.

WARNINGS: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering Librium (chlordiazepoxide hydrochloride) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards. As with all anticholinergic drugs, an inhibiting effect on lactation may occur.

PRECAUTIONS: In elderly and debilitated, limit dosage to smallest effective amount to preclude development of ataxia, oversedation or confusion (not more than two capsules per day initially; increase gradually as needed and toler-

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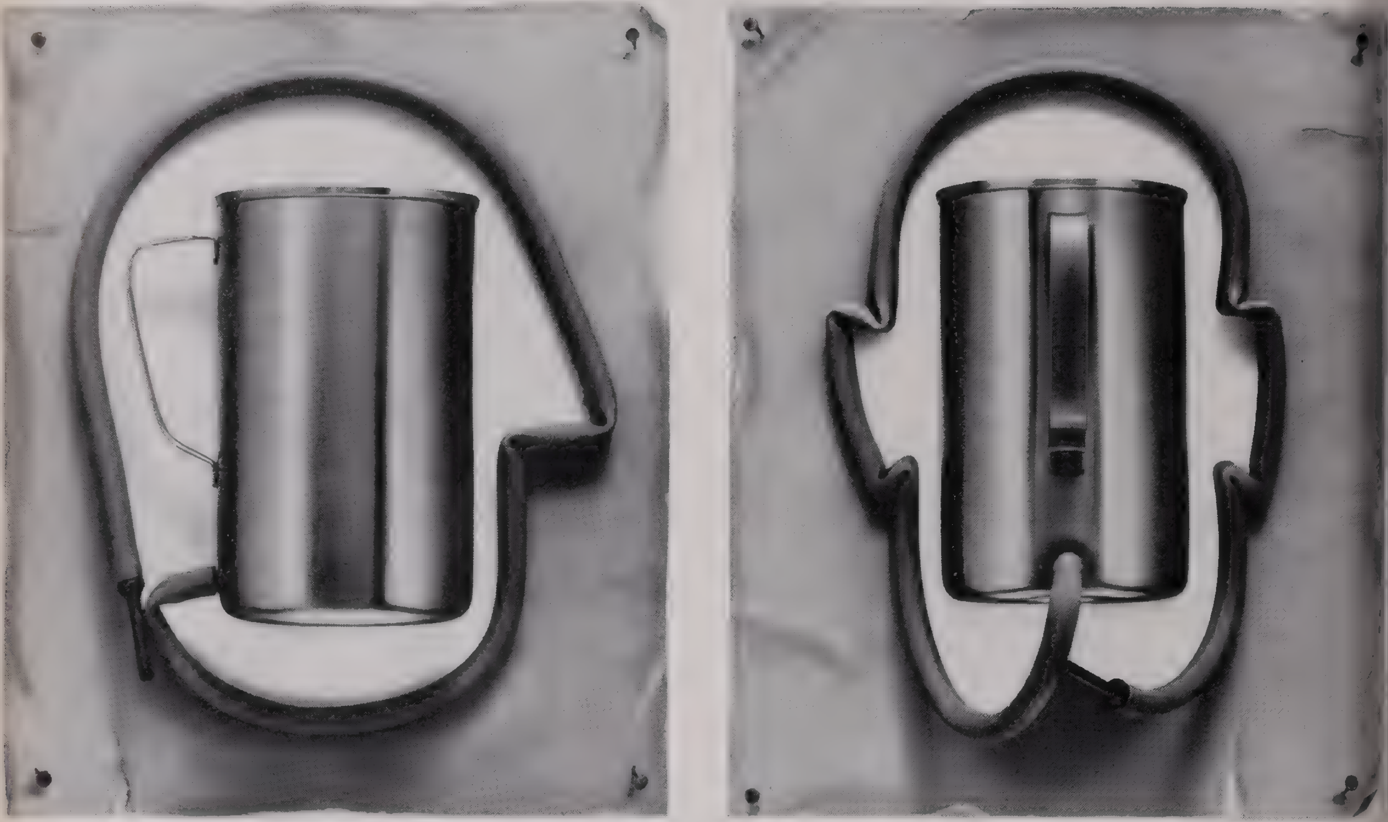

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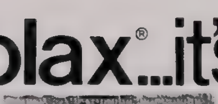

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DU-

Tumor Conference

Glioblastoma Multiforme

RECENT INTEREST in the treatment of glioblastoma multiforme[1,2] prompted a review of the experience at Wilford Hall USAF Hospital, in an attempt to determine the incidence of brain tumors in general, the validity of staging the gliomas and the survivability of the higher stages of astrocytomas; and to determine if there has been any improvement or prolongation of survival by the addition of radiotherapy.

Method

The records of patients diagnosed as having brain tumors, as accumulated in the USAF Central Tumor Registry, were reviewed to determine diagnosis, stage and location, and treatment of the disease. The incidence of the various brain tumors was compared with a series of Cushing[3] and Courville.[4] The quality of survival was determined by the Karnofsky scale[5]; and longevity of survival was calculated on a straight-line formula of number of patients living at five years, divided by the total number diagnosed, for those patients diagnosed prior to 1 July 1963. Patients diagnosed since 1 July 1963 have a calculated length of survival, based on the Berkson and Gage[6] technique for calculation of survival rates and percentages.

Incidence

Table 1 depicts the total number of brain tumor types diagnosed during this period. A comparison of the series from Wilford Hall USAF Hospital with Cajal's and Cushing's series is interesting in several respects. Dr. Cushing obviously saw far more pituitary tumors than either of the other two groups but, in contrast, had very few metastatic tumors in his series, whereas the Wilford Hall and Cajal experiences are almost identical in this regard.

Astrocytoma-Glioblastoma

Table 2 is a further breakdown of the gliomatous brain tumors. The astrocytomas (113; 49.3%) include those with pathologic Grade of I, II, or

III. Sixteen astrocytomas were diagnosed as Grade IV, but are listed with the glioblastoma multiforme. In all three series the astrocytoma/glioblastoma group comprised 72 to 89% of the gliomas, comprising by far the most common type of brain tumor.

Metastatic to the Brain

The second most common brain tumor is that associated with sarcoma or carcinoma metastatic to the brain. A total of 102 patients, comprising 22.4% of the series, were in this category: 12.7% of these patients had metastases from sarcomas; 18.6% developed brain or meningeal involvement from lymphoma/leukemia; and 68.6% had a solid carcinoma metastatic to the brain (Table 3). A subdivision of the carcinoma patients showed that 44% of the brain metastases arose from the lung, followed in decreasing incidence by gastrointestinal tumors, breast carcinoma, and genitourinary tumors.

From Pituitary

The third most common tumor in this series was that arising from the pituitary. It is interesting that in Cushing's series this was the second most common form of brain tumor, while in the Cajal series it was fifth in the order of frequency. Two thirds of the patients with pituitary tumors had chromophobe* adenomas (Table 4). One fourth had eosinophilic tumors, and 13% had mixed or basophilic tumors. This breakdown in tumor type was consistent in the three series.

Other Tumors

Other tumors formed decreasing numbers and percentages of the overall tumors found. A list of frequency of the occurrence of tumors as determined by the Wilford Hall USAF Hospital experience in all age groups shows the astrocytoma to be by far the most common brain tumor, and also by far the most common brain tumor found supratentorially, comprising 135 of the 194 supratentorial tumors. Infratentorial tumors were most commonly astrocytomas (28; 27%), ependymomas (21; 20%), and medulloblastomas (17; 16%). Meningiomas were almost exclusively supratentorial in that 41 of the 44 meningiomas were located over the cerebral hemispheres and only two were found in the posterior fossa. One meningioma was in the third ventricle. All of the medulloblastomas were in the infratentorial region. There were 33 tumors found in the vermis or cerebellar hemisphere, four of them hemangioblastomas, four sarcomas, ten astrocytomas, ten medulloblastomas, and five ependymomas.

Survival

The absolute numbers and survival statistics for patients with various types and grades of gliomatous brain tumors is seen in Table 5.

Ependymoma

Thirty-one patients were diagnosed as having ependymomas, occurring in a variety of locations. Nine originated in the cerebral hemispheres, one on the pons, one in the basal ganglia, and 20 in the posterior fossa. Five of these were in the cerebellum and eleven in the fourth ventricle. The exact location of four could not be determined. These patients had a 20% five-year

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*See Test Your Word Score Page 457.

TABLE 1

	Brain Tumors					
	Wilford Hall Hospital		Cajal		Cushing	
	Number	Percent	Number	Percent	Number	Percent
Gliomatous Brain Tumors	225	49.3	1059	41.4	615	38.5
Metastatic	102	22.4	662	25.9	65	4.1
Pituitary	54	11.8	101	3.9	360	22.5
Meningiomas	44	9.4	349	13.6	271	17.0
Neurinomas	14	3.0	78	3.0	176	11.0
Hemangiomas	7	1.6	235	9.2	41	2.6
Sarcomas	4	0.9	8	0.3	14	0.9
Miscellaneous	7	1.6	66	2.6	56	3.5
TOTAL	457		2558		1598	

TABLE 2

	Gliomatous Brain Tumors					
	Wilford Hall Hospital		Cajal		Cushing	
	Number	Percent	Number	Percent	Number	Percent
Astrocytoma	113	49.3	294	27.7	255	41.4
Glioblastoma	50	23.1	654	61.8	208	33 8
Ependymoma	31	13.8	8	0.8	25	4.1
Medulloblastoma	17	7.6	77	7 3	86	14.0
Oligodendroglioma	10	4.4	12	1.1	27	4.4
Pineal	4	1.8	14	1.3	14	2.3
TOTAL	225		1059		615	

TABLE 3

	Tumors Metastatic To Brain					
	Wilford Hall Hospital		Cajal		Cushing	
	Number	Percent	Number	Percent	Number	Percent
Sarcoma	13	12.7	140	21.2	12	18.5
Lymphoma/Leukemia	19	18.6	—	—	—	—
Carcinoma	70	68.6	522	78.8	53	81.5
*	*	*	*	*	*	*
Lung	31	44.3	265	50.8	—	—
Gastro-intestinal	12	17.1	64	12 3	—	—
Breast	11	15.7	85	16.3	—	—
Genito-urinary	7	10.0	44	8.4	—	—
Other	9	12.8	64	12.3	—	—
TOTAL	102		662		65	

survival, and a median survival of 16.5 months. Location of the ependymoma did not seem to affect the survival or duration of survival in that seven of the 10 patients with supratentorial lesions and 12 of 21 patients with infratentorial lesions expired, with no difference in the median survival of the two groups.

Meningioma

There were 44 patients with meningiomas, having a 69% five-year survival. The meningiomas were primarily located over the cerebral hemispheres, with only two being found in the posterior fossa. Ten patients were diagnosed as having oligodendrogliomas. One patient has lived beyond five years, another three are living less than five years, and six have expired. Eight of the ten oligodendrogliomas were found in a frontal lobe. As expected, all 17 medulloblastomas were located infratentorially. These patients have a poor prognosis, with only 18% surviving five years, the median survival being 17.5 months. Three of the fourteen patients with acoustic neuromas have expired, two as a result of operative mortality and one from a large angle tumor which could not be fully excised. The overall five-year survival rate in this disease is 86%, but 100% if one considers only those patients who survived the postoperative period. This experience is identical to that reported by Ahluwali and Buxton[7] who had an 11% operative mortality in 102 patients with acoustic neuroma.

Astrocytoma

Seventeen patients had astrocytoma Grade I. Twelve are still living for a 74% five-year survival, and a median survival of 46.5 months. All but one of the astrocytomas Grade I were cerebral, the exception being located in the cerebellum. There were 52 with Grade II astrocytoma, 25 of whom are still living, with 35% five-year survival, and 37.5 months median survival. Thirty-four of the 52 patients had supratentorial tumors, the rest being posterior fossa, primarily cerebellar. It is interesting that patients with astrocytoma Grade II, having supratentorial or infratentorial lesions, showed no difference in the length of survival. Forty-four patients had Grade III and 50 patients Grade IV (glioblastoma multiforme) astrocytomas. There were no survivals beyond 39 months in these patients, and the median survival was 5.5 months.

Therapy

Several neurosurgeons have been responsible for the management of these patients; hence the mode of therapy, i.e., surgery, radiation, or surgery plus irradiation, has been totally unselected and purely a reflection of the individual surgeon's opinion of the value of radiation.

Radiation

Table 6 depicts the mode of therapy for the astrocytomas. Those patients treated with radiation alone actually had a biopsy of the tumor, but an attempt to extirpate the tumor would have compromised the patient's quality of survival. The results of therapy in the gliomatous brain tumors revealed that patients with Grade I astrocytomas who were treated with surgery did quite well, living an average of 65 months post treatment.

TABLE 4

	Pituitary Tumors					
	Wilford Hall Hospital		Cajal		Cushing	
	Number	Percent	Number	Percent	Number	Percent
Chromophobe	34	63.0	76	75.0	264	73.3
Eosinophilic	13	24.0	10	10.0	73	20.3
Mixed or Basophilic	7	13.0	15	15.0	23	6.4
TOTAL	54		101			

TABLE 5

	Survival of Patients with Gliomas			
			Survival	
			Duration of Survival in Months	
Type of Tumor	Number Patients	% Surviving 5 Years	Mean	Median
Ependymomas	31	20	33.0	16.5
Meningiomas	44	69	60.4	45.0
Oligodendrogliomas	10	20	40.0	35.0
Medulloblastomas	17	18	23.0	17.5
Acoustic Neuromas	14	86	70.0	39.0
Astrocytoma				
Grade I	17	74	65.0	46.5
Grade II	52	35	40.7	37.5
Grade III	44	0	8.5	6.0
Grade IV	16	0	6.7	4.0
Glioblastoma Multiforme	34	0	8.4	4.5

TABLE 6

Treatment of Astrocytomas/Glioblastomas

	Mode of Treatment							
	No Treatment		Surgery		Radiation		Surg. & Radiation	
Grade of Disease	No.	Duration	No.	Duration	No.	Duration	No.	Duration
Grade I	3	7M	14	65M	—	—	—	—
Grade II	6	1M	20	43M	9	30M	17	48M
Grade III	7	2M	17	7M	3	10M	17	15M
Grade IV	1	2M	11	5M	—	—	4	14M
Glioblastoma Multiforme	8	2M	14	6M	1	1M	11	22M
TOTAL	25		76		13		49	

Surgery and Radiation

Fifty-two patients were diagnosed as having Grade II astrocytomas. Six had biopsies alone with no further treatment and lived an average of one month. Twenty treated with surgery alone had a median survival of 43 months. Nine who had a biopsy followed by irradiation had a 30-month median survival. The 17 patients who were treated with surgery followed by radiation had a median survival of 48 months. Thirty-four of the 52 patients had lesions located in the cerebral hemispheres; nine had cerebellar lesions, and sixteen had infratentorial lesions. There was no difference in the survival of the patients with astrocytoma Grade II, whether the lesion was supra- or infratentorial.

Biopsy Only

Forty-four patients had a Grade III astrocytoma. Seven had a biopsy alone with no further therapy and lived an average of two months. Seventeen treated with surgery alone had a median survival of seven months. Three patients had no biopsy at all. One of these lesions, located in the pons, was treated with irradiation, empirically; of the two patients with basal ganglia lesions, one was treated empirically with irradiation, the other not at all. These diagnoses were later confirmed at autopsy. The median survival of patients treated with radiation alone was ten months. Seventeen treated with surgery followed by irradiation had a median survival of 15 months. In 36 of the 44 patients with astrocytoma Grade III, the lesion was located in the cerebral hemisphere. There were only five patients with infratentorial lesions and, although their survival in each category was quite poor, the number of cases was not large enough to affect the overall duration of survival in this group.

A total of 50 patients were diagnosed as having pathological Grade IV astrocytoma or glioblastoma multiforme. Nine had no treatment and a median survival of two months. Twenty-five were treated with surgery alone, with a median survival of 5.5 months. Only one patient was treated with radiation following biopsy of the lesion. The tumor in this patient was located in the pons and surgical extirpation could not be accomplished. Fifteen patients had surgery followed by irradiation, with a 20-month median survival. Forty-five of these 50 patients had lesions located in the cerebral hemispheres. Only two had cerebellar lesions; three had lesions in the pons. Again, including infratentorial lesions with the rest of the glioblastoma multiforme lesions did not reflect unfavorably upon the overall survival; in fact, the longest duration of survival (39 months) occurred in a patient with a cerebellar lesion which was treated with surgical extirpation followed by irradiation.

Extensive Resection and X-ray

Comparison of the treatment and results in patients with diagnosis of Grade III as compared with Grade IV astrocytoma (glioblastoma) showed no significant difference in the results of these two groups. Therefore Grades III and IV astrocytomas (glioblastomas) could be considered as similar tumors and treated in an identical manner. In Jelsma and Bucy's[1] series of 162 patients, six with glioblastoma lived for longer than three years. Their treatment of choice is extensive resection followed by radiation therapy, since it appears that radiation therapy improves quality of survival for the first 18 months after therapy. Patients who survived longer than 18 months showed no improvement in the quality of survival even with radiation therapy added. Buckley[2] reviews the role of radiation in cerebral gliomas and reports that radiation alone increases length of survival. In his series, patients treated with surgery had a 2.5-month median survival postoperatively; those treated with radiation lived a median of 19.5 months following treatment, and those treated with surgery and radiation had a 12-month median survival.

The present series confirms the fact that patients with astrocytoma Grade I are best treated with surgery alone, and that radiation adds nothing to their survival or quality of survival. Patients with Grade II astrocytoma appear to do well with surgery or surgery plus irradiation, but not as well with radiation alone. In the higher grade astrocytomas, i.e., Grade III or Grade IV (glioblastoma multiforme) patients appear to do best with surgery plus irradiation. It would be our recommendation that patients have a generous internal decompression, followed by x-ray therapy; this will nearly double the survival time of patients with the higher grade astrocytomas. Radiation also prolongs life, even when only a confirmatory biopsy is possible due to the tumor location. Therefore it would be our recommendation that patients with the higher grade astrocytomas be given the benefit of surgical extirpation of the tumor if this is possible without compromising the patients' subsequent quality of survival. This conclusion is in accord with the views of Jelsma and Bucy in their series of 162 patients. This treatment should afford a patient who survives the immediate postoperative period approximately one year of relatively good-quality survival, although the chances of living with any degree of useful function beyond the second year are nil.

Conclusion

Recommendations for treatment of patients with gliomas, particularly the higher grade astrocytomas, are surgery alone for Grade I astrocytoma, surgery plus radiation for Grade II astrocytoma, radiation or surgery plus radiation for patients with Grade III or IV (glioblastoma multiforme) astrocytomas.

Lt. Colonel Fred G. Conrad, USAF, MC*
Colonel Paul Myers, USAF, MC*
Major Richard Buckley, USAF, MC*

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5-7. May be secured from the author or the reprints.

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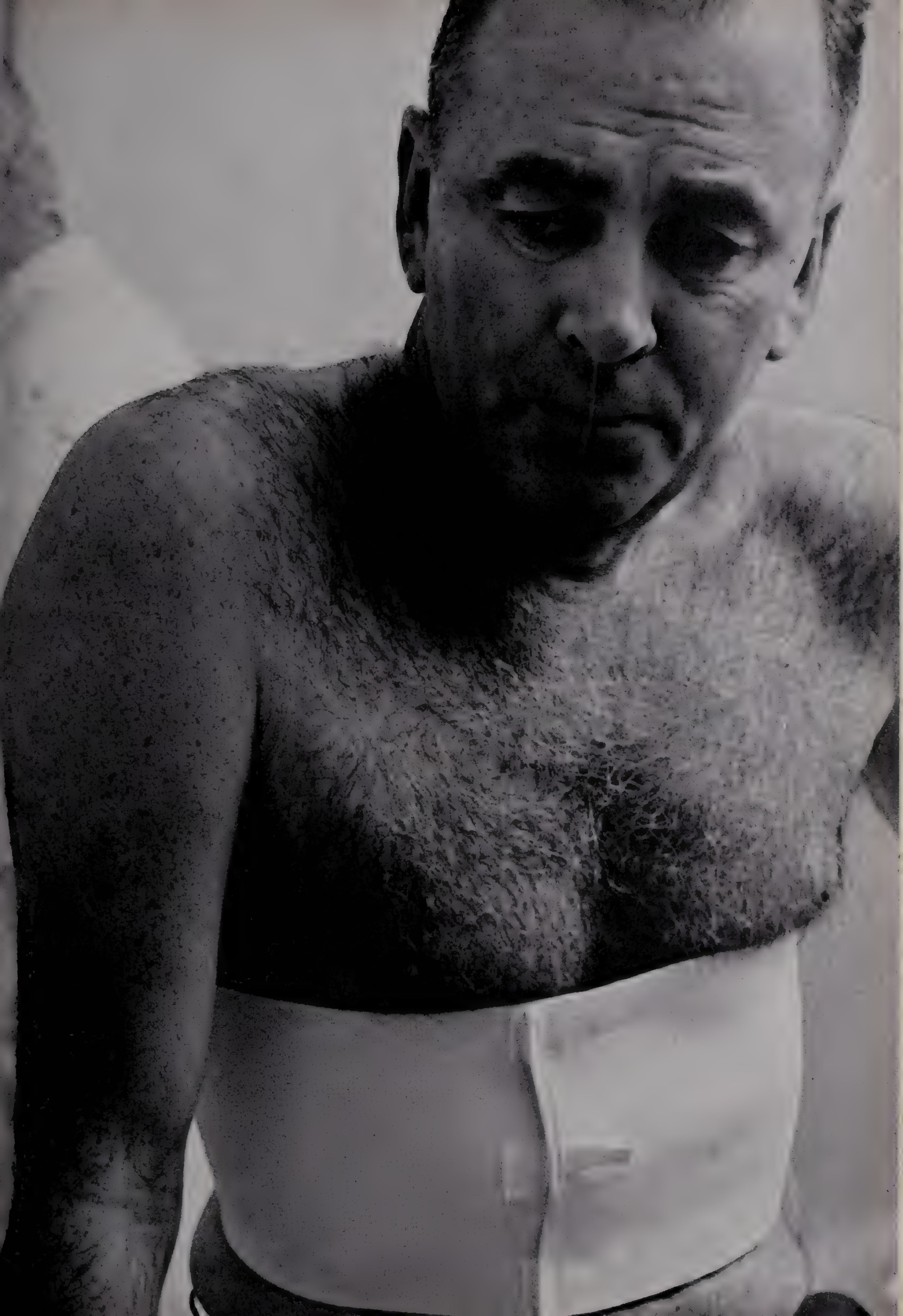

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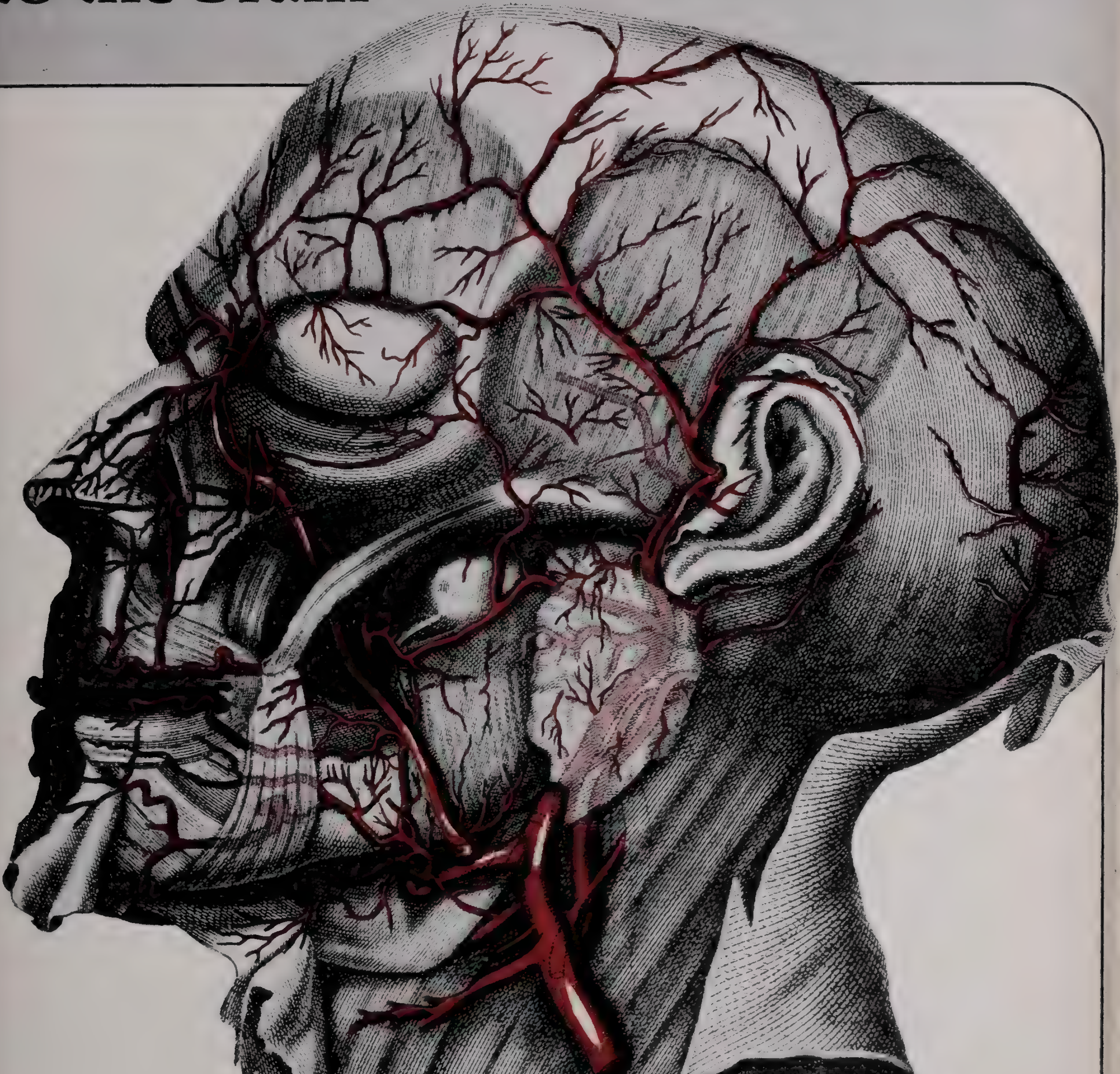

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Doppler Shifted Ultrasound

History and Applications in Clinical Medicine

THE TECHNOLOGY REQUIRED to study blood flow by detection of the Doppler frequency shift in backscattered ultrasound has been developed and reported in the literature during the last 15 years. The basic principles have had several important applications to clinical medicine, largely because the instrument can be used transcutaneously and nondestructively. The purpose of this paper is to review the short history of this new technique, describe the physical principles involved, and discuss the clinical applications.

History

As early as 1957, Satomura, of Osaka University in Japan, adapted Doppler ultrasound engineering principles to the "inspection of cardiac functions."[1] Subsequently, Franklin et al., of the University of Washington School of Medicine, used the Doppler ultrasonic flowmeter in experimental animals.[2] Franklin continued this research at the Scripps Institute, where he adapted the flowmeter to telemetry in order to study blood flow in unrestrained animals.[3] More recently Benchimol and Franklin et al. carried out radio telemetry of human blood flow.[4] Stegal and Rushmer applied the Doppler velocity sensor transcutaneously.[5] Callagan, at the National Naval Medical Center, first undertook detection of the human fetal heart beat by Doppler ultrasonic techniques, and reported it in 1964.[6] Ware, of Southwest Research Institute, described the use of Doppler ultrasonic detection of arterial wall motion (kinetoarteriography) as a means of indirectly determining arterial systolic and diastolic pressures and, in collaboration with several laboratories of the Air Force Systems Command, further developed the system.[7-9]

Technique

The basic principles of the Doppler ultrasonic velocity sensor are fundamental to the various specific applications. Several terms will be used in describing Doppler instruments. *Ultrasound* is defined as any acoustical or mechanical energy that occurs above the limits of human audibility, i.e., usually above 20,000 Hertz (Hz)—one Hz being equal to one cycle per second. Ultrasonic vibrations can be created in the Megahertz (MHz) region by the use of piezoelectric crystals.

Some crystal materials, such as lead zirconate-titanate, exhibit the *piezoelectric effect,* which is the ability of a material to change shape when voltage is applied or, conversely, to create voltage when the crystal shape is deformed.

The *Doppler effect* is the principle by which the frequency is changed when waveform energy is reflected from a moving surface. The change is linear, and it can be additive or subtractive according to whether the reflecting surface is moving toward or away from the source of wave propagation. High frequency ultrasonic waves (0.5 MHz to 15 MHz) penetrate tissue, and reflect from various surfaces, such as blood corpuscles, arterial walls, and surfaces of organs. When 8 MHz ultrasound is reflected from surfaces moving at 0.5 cm/sec to 150 cm/sec, the Doppler shift that occurs is detected and amplified by the instrument, and then presented as a signal within the human audio range.

The instrumentation basic to the Doppler flowmeter is shown in a block diagram (Figure 1). A radio frequency oscillator drives one crystal in a transducer assembly, and a receiver detects the difference in frequency between the transmitted and reflected ultrasound. The output of the receiver is amplified and heard through earphones or a loudspeaker. The pitch of the audio signal is proportional to the velocity of the reflective surface, and the volume is proportional in part to the area of the moving reflective surface. The volume also depends upon the transducer configuration, the angulation of the transducer in relation to the direction of the reflective surface movement, the efficiency of the coupling to the cutaneous surface, and the sensitivity of the equipment. When the system is used as a blood flow detector, it provides an output signal with a frequency that has a linear relationship to blood velocity. Blood flow volume (cc/min) can be determined only when the dimensions of the vessel being studied are known. The dimensions of the lumen seldom are known when the instrument is used transcutaneously.

Basically, the Doppler ultrasonic instrument can provide a sonic or graphic representation of the motion of a reflective tissue surface. The applications of this instrument vary with the type of tissue studied; accordingly, it can be used to detect blood velocity, to determine blood pressure, or to detect a fetal heart beat.

Clinical Uses

The Doppler blood velocity detector employing 5 to 10 MHz ultrasound can be used to evaluate peripheral vascular disease (Figure 2). Used transcutaneously, the instrument lacks the capability of measuring absolute volume flow.

Peripheral Vascular Disease

The clinician uses the instrument in a manner similar to a stethoscope by listening for meaningful sound patterns, which consist of variations in amplitude and pitch. The instrument is remarkably sensitive; it is possible to locate selectively arterial or venous flow in many areas of the body, especially in the extremities. The normal arterial signal recorded from the peripheral arteries has two components: a rise and fall in frequency during systole, followed by a second smaller rise consistent with diastole. Little experience is required for an observer to distinguish velocity signals in stenotic and normal arteries, in arteries proximal and distal to an acute occlusion, and in arteriovenous fistulas. Abnormalities in venous signals also can be detected by the Doppler instrument.[10]

The sensitivity of the equipment allows it to give useful information from otherwise inaccessible arteries, e.g., intercostal arteries. Visceral and deep arteries can be detected, but sometimes anatomical identification is difficult. It is difficult to study intracranial and pulmonary vasculature by this method, for acoustical energy at ultrasonic frequencies is not conducted well by osseous or pulmonary (air-filled) tissue.

When the Doppler ultrasonic instrument is used transcutaneously, the patient experiences neither pain nor discomfort. Although ultrasonic damage to the ciliary body and the cochlea has been reported, it has occurred at very high power levels only.

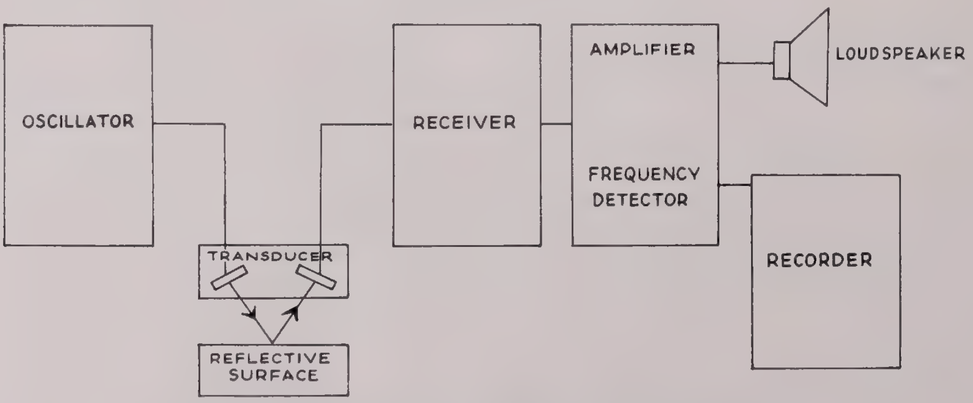

Fig. 1—Block diagram of Doppler ultrasonic flowmeter.

Blood Pressure

Blood pressure can be taken by Doppler ultrasonic techniques. One method of obtaining the systolic blood pressure is to measure the blood flow distal to an occlusive cuff with a Doppler instrument. This procedure is similar to palpating the return of a pulse distal to an occlusive cuff, but is much more sensitive.

An adaptation of the Doppler motion detector makes it possible to determine both systolic and diastolic pressure levels. The transducer is placed under the pneumatic cuff immediately distal to its center and over an artery (Figure 3). The signals resulting from arterial wall motion are emphasized, and the blood flow signals de-emphasized. If the cuff is inflated above systolic pressure levels, the artery remains closed at all times. If the cuff is deflated slowly, when the systolic pressure is reached the artery opens and closes as each pulse wave is allowed to pass. When the pressure is below diastolic levels, the arterial wall movement is not detected.

Taking blood pressure by this method is almost the same as taking it by auscultation of Korotkoff sounds. Instead of listening with a stethoscope over the artery beneath or distal to the cuff, one listens with earphones or a loudspeaker while a special flat transducer is placed under the cuff immediately distal to its center. The endpoints are the same and Doppler sounds appear in manner quite similar to Korotkoff sounds.

Clinical applications of developmental instruments have demonstrated their value for use with patients in shock, for infant blood pressure, and in special situations, such as a high-noise environment.

Fetal Heart Tones

Commercial instrumentation has encouraged widespread use of the Doppler ultrasonic method for determining fetal life. The ultrasonic waves are reflected from the moving fetal cardiac surface (Figure 4): a technique more sensitive than conventional methods, such as the fetoscope and the fetal electrocardiogram. The presence of a fetal heart beat can be detected at 12 weeks of gestation in all patients, and even as early as 10 weeks in some.[11] Multiple gestation can be detected by hearing

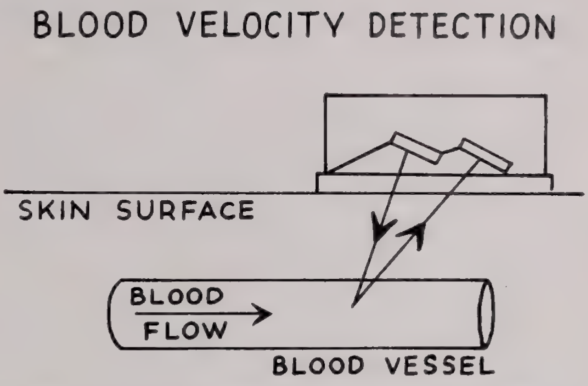

Fig. 2—Use of Doppler apparatus as a blood velocity detector. Ultrasonic beam is reflected from erythrocytes and a shift in frequency is detected.

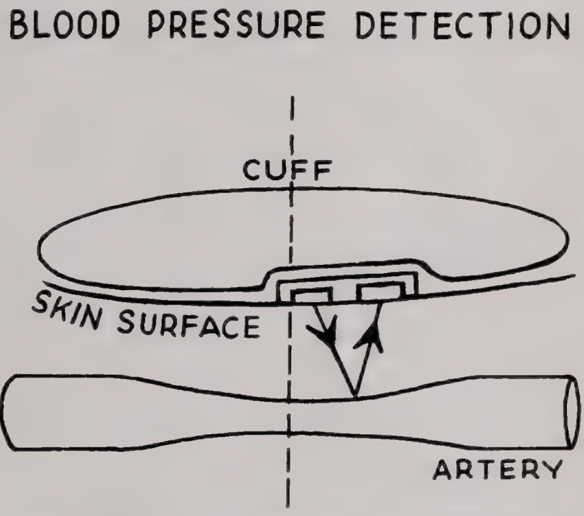

Fig. 3—Use of Doppler apparatus to determine blood pressure. Instrument is used to detect arterial wall motion.

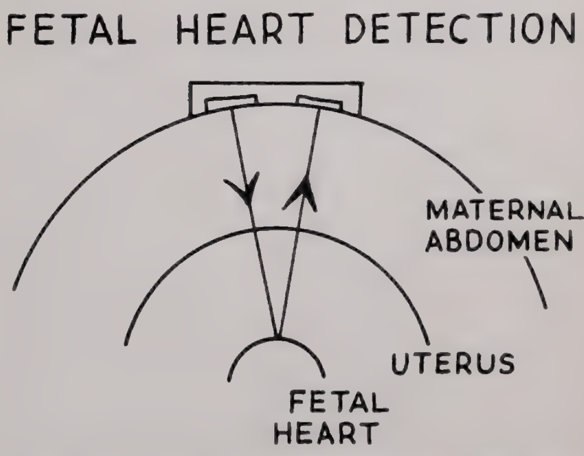

Fig. 4—Use of Doppler apparatus as a fetal heart detector. Ultrasonic waves are reflected from the moving fetal cardiac surface.

more than one heart rate. Another advantage of this method is the ability to localize the placenta from its blood flow pattern. In obstetrical applications, low level 2.5 MHz ultrasound is most widely used without discomfort to the mother or known harm to the fetus.

Comment

The clinical applications described are important to surgeons, pediatricians, obstetricians and anesthesiologists. However, a physician is reluctant to add more "fancy gadgets" to his already immense armamentarium. Preferring to depend upon his senses, aided by the readily available stethoscope, a physician frequently rejects the idea of adopting new diagnostic procedures. Use by the authors of both developmental and commercial Doppler ultrasonic instruments has demonstrated their value in a variety of situations. Equipment available commercially is portable, reliable, and easy to use.

Summary

Japanese and American investigators have applied the Doppler ultrasonic velocity sensor to medicine. Its operation depends upon the use of a pair of piezoelectric crystals which transmit and receive a beam of ultrasound, and incur a frequency shift that is transformed into a discernible audio signal. The Doppler ultrasonic velocity sensor or one of its derivatives has an extensive variety of clinical applications. It can be used to detect fetal heart beats earlier than conventional methods; to aid in diagnosing arterial and venous abnormalities, especially of the extremities; and to determine blood pressure under particularly difficult circumstances. The instrument is easy to operate and causes the patient no discomfort, because it functions transcutaneously.

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William T. Kemmerer, Lt. Colonel, USAF, MC
Michael D. Halber, B.A.*

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A pessimist is one who feels bad when he feels good for fear he'll feel worse when he feels better.—Anonymous

A handful of patience is worth more than a bushel of brains.—Dutch Proverb

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*Medical Student, University of Colorado School of Medicine, Denver, Colorado.

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Clinical Path Conference

Granulomatosis in Infancy and Childhood

Case Presentation

A 27-month-old Japanese-American male was referred to Wilford Hall USAF Hospital from Tachikawa AFB, Japan, because of recurrent pneumonia.

He had been hospitalized at age 15 months for a left lower lobe pneumonia and at age 18 months for a right lower lobe pneumonia, both of which had responded slowly to antibiotics. No causative organisms had been demonstrated. At age 21 months he was admitted because of a persistent, recurrent right lower lobe infiltrate. Although he became afebrile after antibiotic therapy, the infiltrate persisted. A thoracotomy was performed and the right lower lobe was resected. Multiple necrotizing granulomas were found diffusely distributed in the tissue (Figure 1). No organisms were seen in the sections, but cultures grew *Candida* sp. from the lung and *Staphylococci* and *Pseudomonas* sp. from the trachea. He recovered uneventfully from the operation and was discharged on no medication. Four months later, a right middle lobe infiltrate appeared.

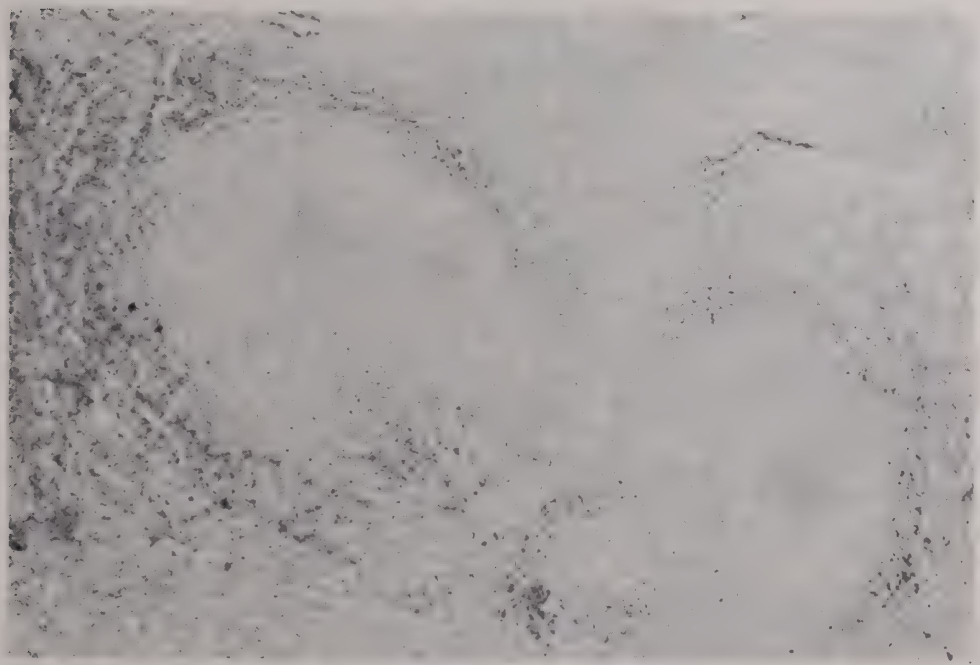

Fig. 1—Granulomas in right lower lobe of lung (100 X).

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Past History

The patient was the product of a normal pregnancy. His birth weight was eight pounds, nine ounces. At nine months of age, bilateral incision and drainage of cervical lymph nodes was done (results of cultures not available). He had suffered from a severe but poorly described skin rash the previous summer and had had otitis media at ages two and 11 months.

Family History

Family history revealed that a male sibling had died at age three months of pneumonia, and an eight-year-old male sibling was alive and well.

Examination

On admission, physical examination revealed a 62 cm, 12.2 kg, irritable male whose temperature was 98.2° F, pulse 140, and respirations 40/min. Healed bilateral cervical scars and a right thoracotomy scar were present. There was mild respiratory distress and he was retracting bilaterally at the bases. The heart was of normal size without murmurs. The abdomen was soft without organomegaly. There was no lymphadenopathy. The tonsils were present and normal.

Laboratory Studies

The urinalysis was normal. The hematocrit was 32% with 10 gm% hemoglobin. Total white blood cell count was 15,900 with 57% neutrophils and 43% lymphocytes. Erythrocyte sedimentation rate (Westergren) was 52 uncorrected and 25 corrected. Serum sodium was 143 mEq/L, potassium 5.1 mEq/L, chlorides 103 mEq/L and bicarbonate 17 mEq/L. Sweat sodium was 7 mEq/L and the chlorides were 2 mEq/L.

Serum protein electrophoresis revealed a total protein of 7.1 gm% with albumin 3.1 gm%, alpha—1 globulin 0.3 gm%, alpha—2 globulin 1.0 gm%, beta—globulin 1.0 gm% and gamma—globulin 1.7 gm%. Immunoglobulin levels were: IgG—1240 mg% (nl range—600 to 1000 mg%), IgA—788 mg% (nl range—112 ± 41) and IgM—109 mg% (mean—116). Titers against typhoid O and H were less than 1:80 on admission and rose to 1:80 and 1:160, respectively, after a typhoid booster. Delayed hypersensitivity response was normal as measured by DNFB skin testing. Skin tests for fungi and tuberculosis (intermediate PPD) were negative. A Kveim test was negative. The blood group was AB.

A liver biopsy disclosed no abnormalities. Examination of the bone marrow showed a granulocytic hyperplasia with a mild increase in plasma cells and eosinophils. Cultures of the marrow were negative.

Progress

The patient remained relatively asymptomatic until one month after admission, when he began to spike fevers to 104° F, and decreased breath sounds were heard over the right lung base. Chest films showed the persistent right middle lobe infiltrate with a pleural effusion. Penicillin therapy was begun. Attempts at thoracentesis were unsuccessful.

One week later, a right middle lobe lobectomy was done. Chronic necrotizing granulomatous inflammation similar to that found in the right lower lobe was seen. No organisms were found in the tissue, but Aerobacter-Klebsiella was cultured.

Two days after surgery, the patient's temperature returned to normal, and a three-pound weight gain was noted over the next week. Dehiscence of the thoracotomy incision occurred on the seventh postoperative day. Kanamycin was given for 14 days postoperatively. The incision did not heal, but his condition remained otherwise stable and he was discharged on the 61st hospital day on no medications.

Admission Seven Months Later

The patient remained relatively well following discharge except for periodic unexplained fevers which were treated with Ampicillin. Two weeks prior to admission, fever was noted and his appetite decreased.

Physical examination revealed a chronically ill, irritable child with nuchal rigidity and an open thoracotomy wound. The temperature was 101.6° F, the pulse 100, and respirations 36. The weight was 13.7 kg. The cerebrospinal fluid was clear and no cells were found. Pressure was not measured. The glucose was 56 mg% and the protein 90.8 mg%. A blood glucose was not done. Cultures, gram stain and India ink preparations were negative.

The fever subsided but the nuchal rigidity persisted. Three weeks later the temperature was 101° F and hyperactive deep tendon reflexes and a positive Babinski on the left were noted. No papilledema was found. The white blood cell count was 24,000 with 67% neutrophils, 1% bands, 25% lymphocytes and 7% eosinophils. The hematocrit was 37% with a hemoglobin of 11.1 gm%. Cultures of the throat, urine, bone marrow, and spinal fluid for bacteria, acid-fast bacilli and fungi were negative. Skin tests for tuberculosis and fungi remained negative. A chest film showed a right pleural effusion with a shift of the mediastinum to the left and a right upper lobe pneumonia. An electroencephalogram was interpreted as "abnormal—generally slow." A brain scan was normal. A ventriculogram showed minimally dilated lateral ventricles. The opening pressure of the ventricular fluid was 600 mm of water. A cell count was 1100/mm^3 with 69% polymorphonuclear and 31% lymphocytes. The protein was 34 mg% and the glucose was 58 mg%.

Treatment with isoniazid, para-amino salicylic acid and streptomycin was begun on an empirical basis. His condition remained essentially unchanged until two weeks later when a 4-cm fluctuant mass was noted in his right upper mid-back. Physical examination showed blurring of the optic discs bilaterally but was otherwise unchanged. Total white blood cell count was 16,600 with a normal differential. Blood urea nitrogen was 6 mg% and repeated urinalyses were normal. Cultures of the spinal fluid, throat, urine and stool were negative. Complement fixation tests for Histoplasmosis were 1:64 and for Coccidioidomycosis were 1:32.

An incision and drainage of the back mass was done and cultures revealed *Aspergillus fumigatus*. Amphotericin B was administered intravenously at a dose of 10 mg/kg over a period of three weeks. Spiking fevers and several episodes of seizure activity characterized by opisthotonus developed. His condition slowly deteriorated and he expired two months after admission.

Discussion

Dr. Edgar O. Ledbetter:*

In summary, this boy had otitis media, severe dermatitis and cervical adenitis during his first year, was plagued by chronic, recurrent lobar pneumonia throughout his second and third years, and despite the administration of a wide variety of antimicrobial agents he expired at age 40 months with lobar pneumonia and severe encephalomyelitic signs. A male sibling had died of pneumonia in early infancy.

Deficiency Syndromes

The various antibody deficiency syndromes were excluded by the demonstration of typhoid antibody production, the presence of abundant plasma cells in the bone marrow, his capacity to develop delayed hypersensitivity, and elevated serum immunoglobulin levels.

The Wiskott-Aldrich syndrome was suggested by the family history, dermatitis, recurrent infection, and elevated serum IgA levels; but thrombocytopenia and hemorrhagic diatheses were not mentioned. Isohemagglutinins have been low or absent in patients with this syndrome but would not have been helpful since his blood type was AB.

Hypergammaglobulinemia is frequently found in children with chronic infection and may be present in patients with histiocytosis-X or sarcoidosis, both of which were excluded by the pathology of the resected lung tissue. Sarcoid granulomas show little or no necrosis and tend to remain discrete rather than becoming confluent. Hilar lymph node enlargement is usually striking. In contrast with the lobar involvement present in this patient, diffuse cystic or nodular pulmonary infiltrates are characteristic of histiocytosis-X; necrosis and granuloma formation are uncommon.

The differential diagnosis is limited in this patient by the findings of granulomatous lobar pneumonia and the chest wall mass from which *Aspergillus fumigatus* was cultured.

Fungus Infections

Soft tissue abscesses may occur with any of the fungal infections, being more common in actinomycosis and coccidioidomycosis. Actinomycosis requires anaerobic incubation for growth. Other organisms such as anaerobic streptococci and various aerobic and anaerobic gram-negative bacilli are frequently found in the suppurative drainage of actinomycotic abscesses. Spherules can often be demonstrated in wet preparations of material aspirated from soft tissue abscesses caused by coccidioidomycosis.

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*Department of Pediatrics, Wilford Hall USAF Hospital.

"Cold" staphylococcal abscesses involving the skin, subcutaneous tissue, lungs or mastoids have been reported in children without demonstrable predisposing systemic disease (Job's syndrome), but there was no culture evidence for staphylococcal infection in this patient's chest mass.

Central nervous system invasion is a frequent complication of pulmonary nocardiosis, cryptococcosis and mucormycosis occurring less often with actinomycosis and aspergillosis. These organisms may be extremely difficult to demonstrate in the spinal fluid; and negative cultures, smears, and India-ink preparations do not rule out fungus infection.

A. fumigatus is a frequent laboratory contaminant with worldwide distribution. Most infections by this and other opportunistic pathogens are seen in patients with leukemia, lymphoma, diabetes mellitus, and hypogammaglobulinemia or in patients receiving corticosteroids, antimetabolites, immunosuppressives, and/or antimicrobials. Pulmonary mycetomas secondary to *A. fumigatus* are usually found in association with destructive lung disease of some other etiology, such as cavitary tuberculosis. The soft tissue mass from which *A. fumigatus* was grown was evidence of dissemination, most likely from the lungs, and Aspergillus meningoencephalitis could explain this boy's central nervous system abnormalities. Although we cannot be sure that his cerebrospinal fluid glucose levels were normal, since simultaneous blood glucose determinations were not available, normal cerebrospinal fluid glucose levels have been present in other cases of Aspergillus meningitis.

Familial Granulomatous Disease of Childhood

The failure to demonstrate organisms in the sections of the lobectomy specimens leaves the etiology of the earlier pulmonary granulomas in question. Except for the absence of hepatosplenomegaly, this child's chronic granulomatous process and clinical course resembled fatal (chronic) granulomatous disease of childhood first reported by Berendes et al. This familial entity is characterized early by recurrent suppurative lymphadenitis and chronic dermatitis, followed by chronic progressive pulmonary disease and hepatosplenomegaly. Caseous granulomas are usually found in the lymph nodes, liver, spleen and lungs. Pigmented lipid histiocytes have been demonstrated in the lymph nodes, liver, spleen, thymus, and intestinal tract, but have not been found in involved lung tissue (Figure 2). Although these periodic acid-Schiff-positive lipid histiocytes are not pathognomonic for this disease, they have been prominent in most reported cases.

The cause for chronic granulomatous disease of childhood has not been determined. No immunologic deficiencies have been recognized among the reported cases. Gamma globulin levels are consistently elevated. The serum levels of IgG, IgM, and IgA have been variable, but one or more of these three components has been disproportionately increased in several patients. Defective bactericidal function and metabolic abnormalities of polymorphonuclear leukocytes from these patients have been demonstrated. Although their polymorphonuclear leukocytes appear morphologically normal, are present in adequate numbers, and are able to migrate and phagocytose bacteria, their intracellular bactericidal activity against certain organisms, including *Staphylococcus aureus* and *Serratia marcescens,* is reduced. These leukocytes, however, have been shown to retain their bactericidal capacity for various streptococci. This disease can now be differentiated from other granulomatous diseases in children by the nitro-blue tetrazolium reduction test, an in-vitro leukocyte function test which allows recognition of abnormal leukocytes in the patients with the disease as well as in the female carriers.

Patients with chronic granulomatous disease of childhood are commonly infected by organisms of an avirulent and relatively non-invasive type such as were cultured from the patient presented, i.e., Staphylococci, Pseudomonas, Aerobacter-Klebsiella, Candida, and Aspergillus. For reasons unknown, children with chronic granulomatous disease of childhood develop granulomas in response to infection by these organisms, just as a normal person's tissue responds to the organisms which cause tuberculosis and brucellosis. Pneumococcal, streptococcal and Hemophilus infections have been rare.

Histoplasmosis and coccidioidomycosis have not been reported in patients with chronic granulomatous disease of childhood. The rise in this patient's histoplasmin and coccidioidin complement fixation titers may have been the result of repeated skin testing with these antigens.

Infections tend to be chronic and recurrent in children with this hereditary defect of leukocyte function, and prolonged specific antimicrobial therapy is required for their control. Despite vigorous treatment of their infections, most children have a fatal outcome in early childhood.

Clinical Diagnosis

1. Fatal (chronic) granulomatous disease of childhood.
2. Pulmonary aspergillosis with subcutaneous and central nervous system dissemination.

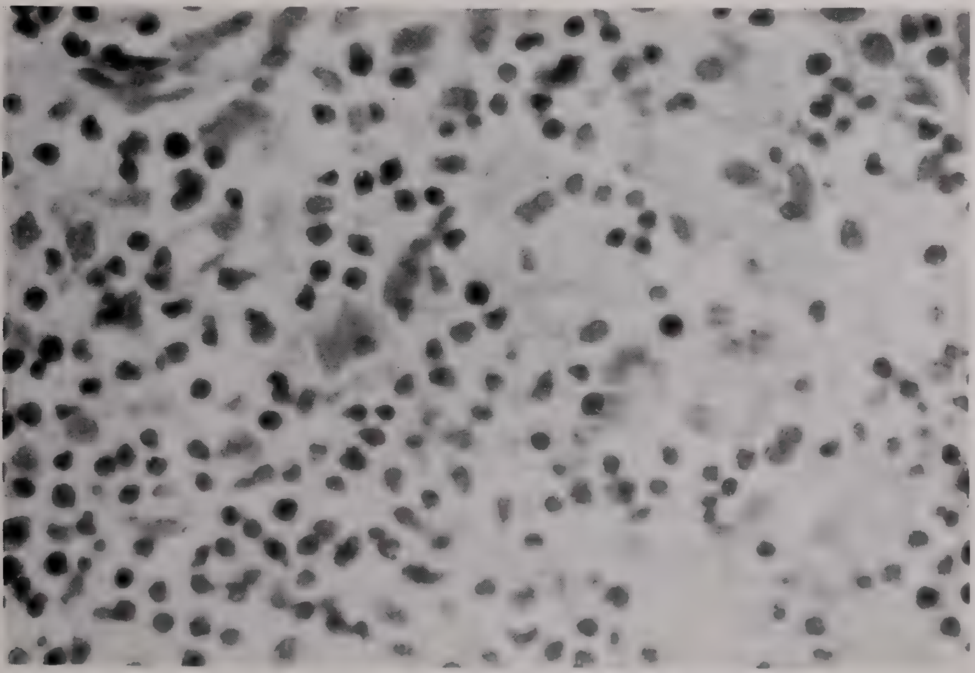

Fig. 2—Pigmented lipid histiocytes in lymph node (Periodic acid-Schiff Stain. X 430).

Comments

Dr. Howard H. Johnson:*

Have the female cases reported been familial?

Dr. Ledbetter:

Most cases reported have been in boys. Leukocyte function studies of affected families provide evidence that the disease is usually transmitted as an X-linked recessive trait. The mode of inheritance for the female cases has not been definitively established. Family members of the female cases have not been found to be affected.

Dr. Howard F. Koch:†

What organ systems other than the lungs are commonly involved with infection in children with this disease?

Dr. Ledbetter:

Osteomyelitis, pericarditis, hepatic abscesses and perirectal abscesses have been present in several reported cases.

Dr. George S. Fidone:‡

How effective is amphotericin B in the treatment of aspergillosis?

Dr. Ledbetter:

Treatment of Aspergillus infections with amphotericin B and other agents available has been unsuccessful. Surgical resection, when feasible, has been the only effective mode of treatment.

Pathological Discussion

Dr. Richard W. Ransom:#

At autopsy, the patient was extremely cachectic, weighing only 12.7 kg. The thoracotomy wound and the ulcerated mass on the back showed no evidence of healing, but no gross pus was present.

The right pleural cavity was obliterated by dense fibrous adhesions. No fluid was found. The right upper lobe showed broad bands of fibrous tissue and a few scattered yellow-brown granular areas in the parenchyma, and the pleura was covered with a gray-green shaggy membrane. A single necrotizing granuloma was found microscopically. No pigmented lipid histiocytes were seen. Sections from the right lung near the thoracotomy incision showed branching, septate hyphae consistent with Aspergillus sp. (Figure 4). The left lung was normal at autopsy.

The spleen weighed 100 grams (normal range for age: 37-39 grams). The cut surface was marked by a diffuse fine, golden-brown granularity. Microscopically, multiple necrotizing granulomas were seen. Large numbers of pigmented lipid histiocytes were present at the periphery of the granulomas. No organisms were found.

There was a diffuse lymph node hyperplasia and the majority of the nodes contained focal areas of yellow-green granularity. A single mesenteric node contained a cluster of 1-3 micra rounded organisms in macrophages demonstrated with the Gomori methenamine silver stain (Figure 3). Pigmented lipid histiocytes were abundant in the nodes (Figure 2).

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#Senior Resident, Department of Pathology, Wilford Hall USAF Hospital.

The granulomas in all organs showed an outer rim of plasma cells, histiocytes and fibroblasts with a central area of polymorphonuclear leukocytes and nuclear debris.

The thymus weighed one gram and was involuted. The adrenals were somewhat atrophied also.

The brain weighed 1300 grams (normal range for age: 1141 - 1191 grams). The cerebral hemispheres showed marked flattening and widening of the gyri. The meninges over the hemispheres were clear but the basilar

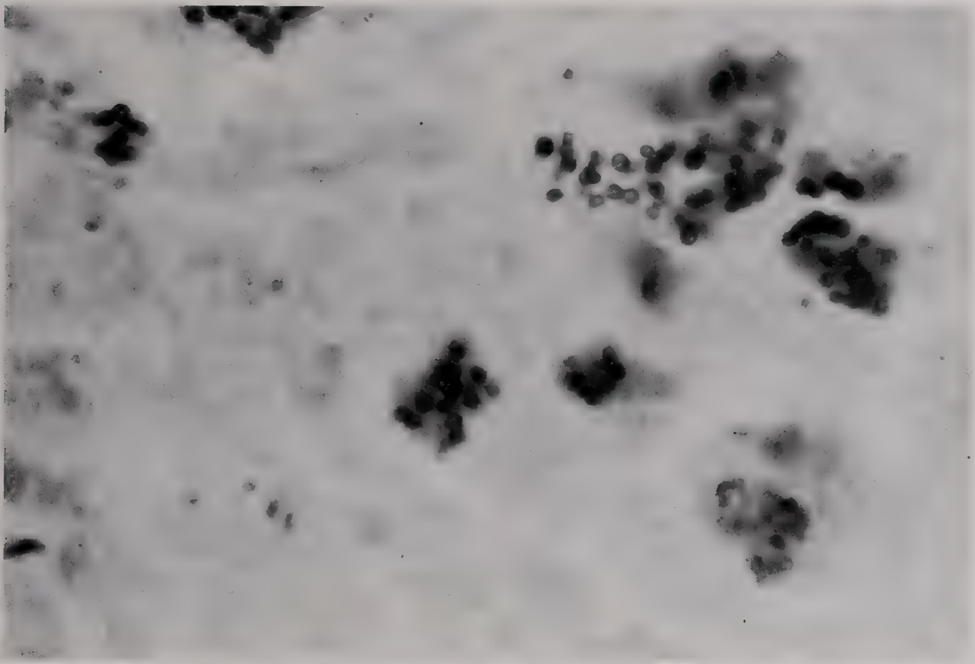

Fig. 3—Unidentified organisms in mesenteric lymph node (Gomori methenamine silver stain. X 970).

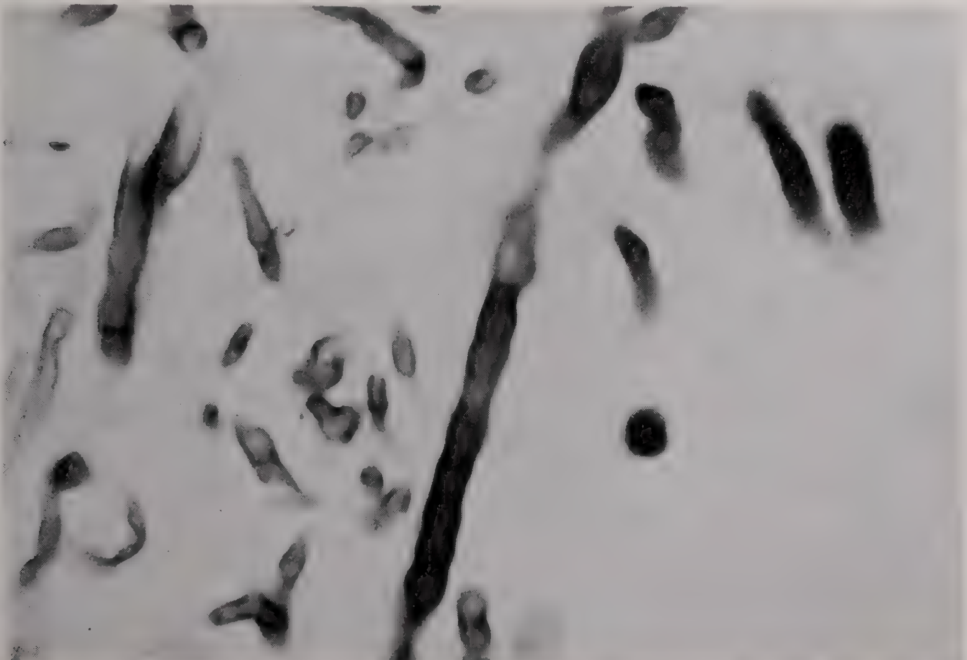

Fig. 4—Branching septate hyphae (*Aspergillus fumigatus*) in meninges of cervical spinal cord. (X 970).

meninges were thickened and opacified. A subarachnoid collection of yellow purulent material was found at the base of the cerebellum. On sectioning the brain, marked dilatation of the ventricular system was apparent. Focal accumulations of yellow exudate were found throughout the ventricular system. The cervical spinal cord also showed marked thickening of the meninges and accumulations of purulent material. Sections from the fourth ventricle and spinal cord stained with the Gomori methenamine silver stain showed organisms similar to those in the pleura (consistent with *Aspergillus* sp.). No bacteria were demonstrated in the tissue, although *Staphylococcus aureus* and *Escherichia coli* were cultured from the cerebellum and spinal fluid at autopsy.

The remainder of the organs were essentially normal. The liver was within normal weight range (502 grams) and showed no granulomas, although there was a diffuse, predominantly portal, infiltrate of pigmented lipid histiocytes.

Dr. Ledbetter:

The absence of hepatosplenomegaly in this case is unusual and may be explained by the relatively short duration of his illness. It is assumed that his liver would have been enlarged had he lived longer.

Final Anatomic Diagnoses

Morphologic findings consistent with Fatal (Chronic) Granulomatous Disease of Childhood.

Secondary systemic infection with *Aspergillus* fumigatus with meningitis, obstructive hydrocephalus and cerebral edema.

Unidentified organisms in mesenteric lymph node—? *Histoplasma capsulatum* — ? *Pneumocystis carinii* — ? conidia of *Aspergillus*.

Edgar O. Ledbetter, Lt. Colonel, USAF, MC*
Richard W. Ransom, Major, USAF, MC*

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*From the Departments of Pediatrics and Pathology, Wilford Hall USAF Hospital, Lackland Air Force Base, Texas.

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Wisdom

To be wise you should read the newest books in science and the oldest in literature. —*Anon.*

Wife

Try praising your wife, even if it does frighten her at first.—Billy Sunday

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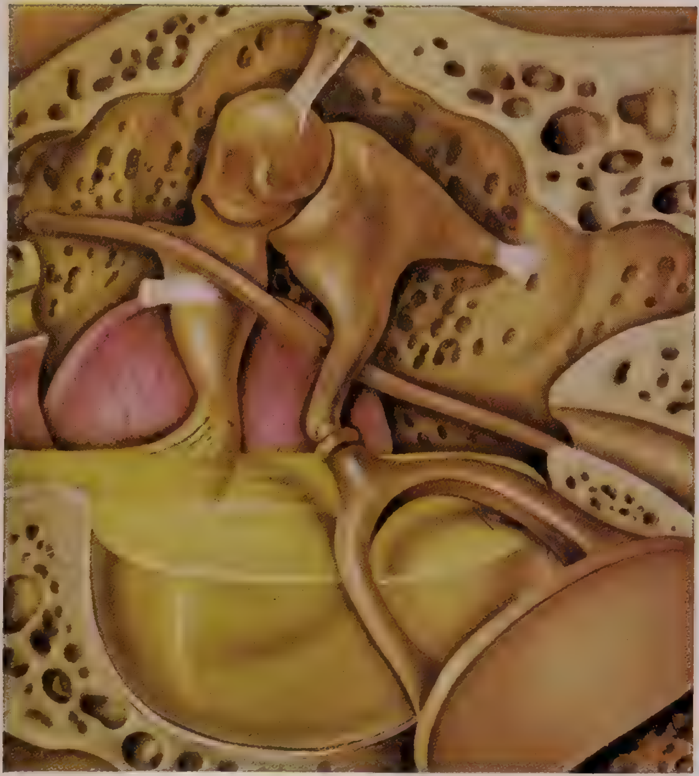

You've made it one of your specific in acute otitis media

DECLOMYCIN acts against many strains of H. influenzae, pneumococci and streptococci, the most common invaders. In otitis media, where it is difficult to isolate the causative organism, this coverage may be important. However, some strain may be resistant and other pathogens can be involved.

You've found the high serum levels of DECLOMYCIN important, too. Its prolonged actio permits convenient 300 mg b.i.d. or 150 mg q.i.d. administration.

When specimens are obtainable, your culture studies will indicate the usefulness of DECLOMYCIN.

Effectiveness: DECLOMYCIN Demethylchlortetracycline should be equally or more effective therapeutically than other tetracyclines in infections caused by organisms sensitive to the tetracyclines.

Contraindication: History of hypersensitivity to demethylchlortetracycline.

Warning: In renal impairment, usual doses may lead to excessive accumulation and liver toxicity. Under such conditions, lower than usual doses are indicated, and, if therapy is prolonged, serum level determinations may be advisable. A photodynamic reaction to natural or artificial sunlight has been observed. Small amounts of drug and short exposure may produce an exaggerated sunburn reaction which may range from erythema to severe skin manifestations. In a smaller proportion, photoallergic reactions have been reported. Patients should avoid direct exposure to sunlight and discontinue drug at the first evidence of skin discomfort. Necessary subsequent courses of treatment with tetracyclines should be carefully observed.

Precautions: Overgrowth of nonsusceptible organisms may occur. Constant observation is essential. If new infections appear, appropriate measures should be taken. In infants, increased intracranial pressure with bulging fontanels has been observed. All signs and symptoms have disappeared rapidly upon cessation of treatment.

Side Effects: Gastrointestinal system—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocoliti pruritus ani. Skin—maculopapular and erythematous rashes; a rar case of exfoliative dermatitis has been reported. Photosensitivit onycholysis and discoloration of the nails (rare). Kidney—rise in BU apparently dose-related. Transient increase in urinary output, some times accompanied by thirst (rare). Hypersensitivity reactions—urt caria, angioneurotic edema, anaphylaxis. Teeth—dental staining (ye low-brown) in children of mothers given this drug during the latter ha of pregnancy, and in children given the drug during the neonatal per od, infancy and early childhood. Enamel hypoplasia has been seen i a few children. If adverse reaction or idiosyncrasy occurs, discontinu medication and institute appropriate therapy. Demethylchlortetra cycline may form a stable calcium complex in any bone-forming tissu with no serious harmful effects reported thus far in humans.

Average Adult Daily Dosage: 150 mg q.i.d. or 300 mg b.i.d. Shoul be given 1 hour before or 2 hours after meals, since absorption i impaired by the concomitant administration of high calcium conte drugs, foods and some dairy products. Treatment of streptococc infections should continue for 10 days, even though symptoms hav subsided.

DECLOMYCIN®
DEMETHYLCHLORTETRACYCLINE

Capsules: 150 mg; **Tablets:** film coated, 30 mg, 150 mg and 75 mg of demethylchlortetra cycline HCl.

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Butisol SODIUM®
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the "daytime sedative" for everyday situational stress

When stress is situational—environmental pressure, worry over illness—the treatment often calls for an anxiety-allaying agent which has a prompt and predictable calming action and is remarkably well tolerated. Butisol Sodium (sodium butabarbital) meets this therapeutic need.

After 30 years of clinical use . . . still a first choice among many physicians for dependability, safety and economy in mild to moderate anxiety.

Contraindications: Porphyria or sensitivity to barbiturates.

Precautions: Exercise caution in moderate to severe hepatic disease. Elderly or debilitated patients may react with marked excitement or depression.

Adverse Reactions: Drowsiness at daytime sedative dose levels, skin rashes, "hangover" and systemic disturbances are seldom seen.

Warning: May be habit forming.

Usual Adult Dosage: As a daytime sedative, 15 mg. (¼ gr.) to 30 mg. (½ gr.) t.i.d. or q.i.d.

Available for daytime sedation: Tablets, 15 mg. (¼ gr.), 30 mg. (½ gr.); Elixir, 30 mg. per 5 cc. (alcohol 7%).

BUTICAPS® [Capsules Butisol Sodium (sodium butabarbital)] 15 mg. (¼ gr.), 30 mg. (½ gr.).

McNEIL

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If you think the pink pill for U.R.I. symptoms is built for speed and endurance you're on the right track.

Here is a tablet that begins to relieve symptoms of upper respiratory infection quickly—a tablet that works for hours to make it easy for your patient to enjoy continuous relief.

Novahistine Singlet combines effective dosage of an antipyretic-analgesic with a vasoconstrictor-antihistamine formulation to relieve not only the congestion, but also the fever and the aches and pains that almost always accompany upper respiratory infections.

A total daily dosage of 3 or 4 tablets will normally provide the continuous relief your patient expects. Use with caution in patients with severe hypertension, diabetes mellitus, hyperthyroidism or urinary retention. Caution ambulatory patients that drowsiness may result.

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Novahistine® Singlet decongestant-analgesic

(Each tablet contains: phenylephrine hydrochloride, 40 mg.; chlorpheniramine maleate, 8 mg.; acetaminophen, 500 mg.)

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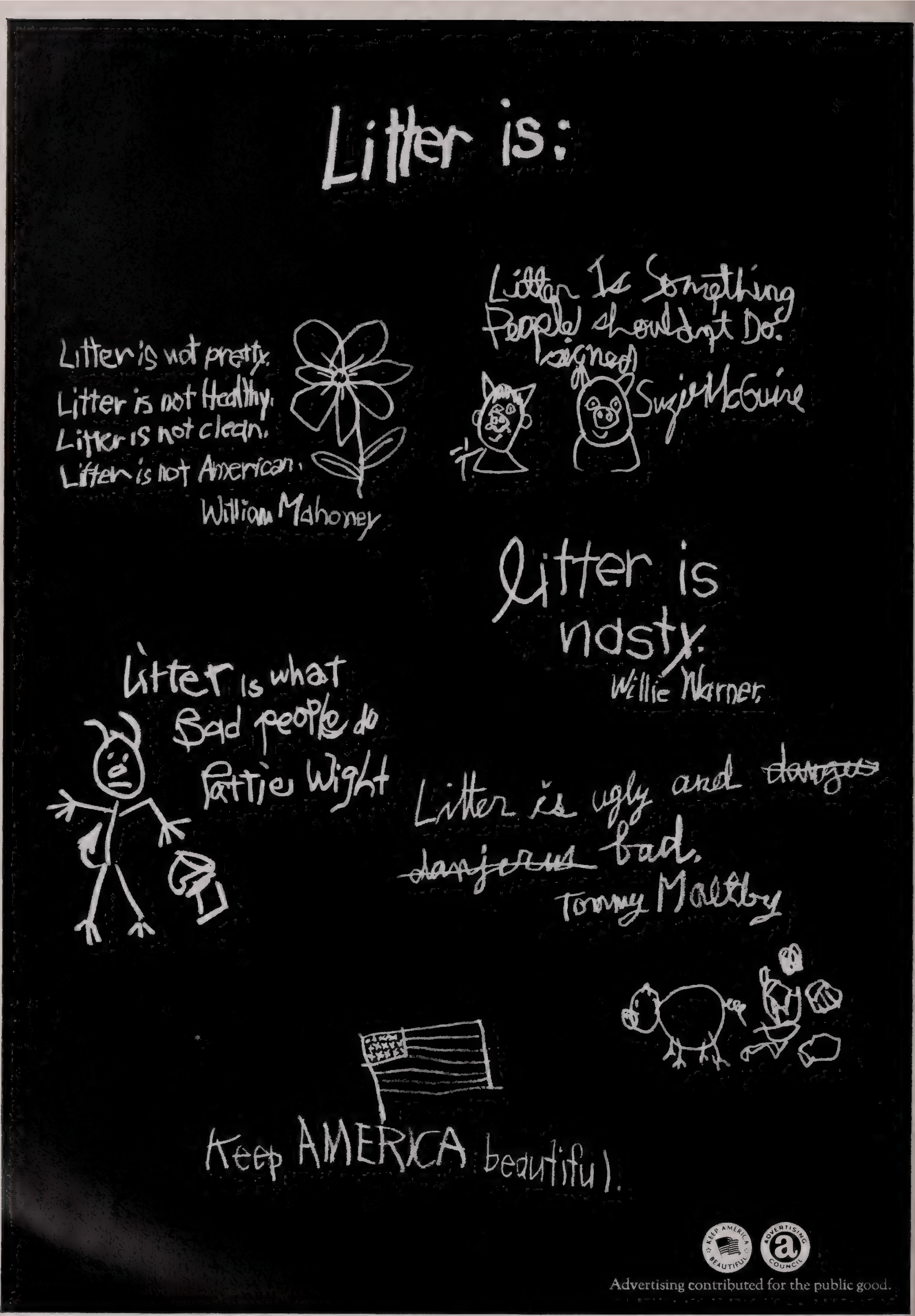

Litter is:

Litter is not pretty.
Litter is not Healthy.
Litter is not clean.
Litter is not American.
William Mahoney

Litter Is Something People shouldnt Do.
signed Suzie McGuire

litter is nasty.
Willie Warner.

Litter is what Bad people do
Pattie Wight

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Tommy Maltby

Keep AMERICA beautiful.

Advertising contributed for the public good.

Grand Rounds

Left Atrial Myxoma

Historical Perspective

Dr. Eliot Schechter:*

Medical writing regarding cardiac tumors dates historically from a comment of Senac[1] in 1783 that "the heart is too noble an organ to be attacked by a primary tumor." The pathologist first showed him wrong. Only recently (1952) the first preoperative or ante-mortem diagnosis of a myxoma in the heart was made. The first successful surgical removal of a myxoma was not until 1955, although some attempts had been made earlier. This lesion is seen in .05% (five out of 10,000) of autopsies. Clinically, it is diagnosed even less frequently. The importance of today's discussion is that a recognized myxoma is a curable lesion; yet, like many things in medicine, if you don't think about a diagnosis you'll never recognize it. It is important for those of us who see patients to be aware of myxoma so that, although rare, we can recognize and treat it appropriately.

The stimulus for today's discussion is a patient who was referred here several weeks ago.

Case History

Dr. James Kay:†

The case is that of a 34-year-old white male who was admitted to Wilford Hall USAF Hospital on 14 April 1968. His present illness dates from 1 April 1968. At that time he was riding horseback and experienced some nausea, which he thought was related to the horseback riding. Over the next few minutes, he developed some abdominal discomfort and then a feeling of weakness in his legs, which shortly progressed to a feeling of numbness and tingling. He felt that his legs were very cold. He was taken to the Emergency Room at Clark Air Base where physical examination revealed pale, pulseless lower extremities bilaterally. An aortogram done immediately revealed nonvisualization of the terminal aorta. He was taken to the operating room where the bifurcation of the aorta was exposed through a lower midline abdominal incision, and approximately 60 cc of blood clot, containing tissue, was removed. The left lower extremity pulses remained poor, and a left femoral incision was made with removal of approximately 10 cc of clot from the left femoral artery.

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Past history revealed that for approximately three years prior to this illness he had noticed soreness and tightness in both legs, primarily in the calves. He stated that after playing volleyball or basketball he would get cramps in his legs, often lasting three to four weeks. Approximately one year before, he had had a similar episode; he was swimming and noted weakness and tingling in the right calf area. This quickly disappeared with rest and he thought no more of it.

Comments

Dr. Schechter:

There are a couple of points to emphasize in the history. Emboli are frequent; about 40% of patients with myxomas have them. Most arise from myxomas in the left atrium and are peripheral emboli, but right atrial myxomas can produce pulmonary emboli, and occasionally a left ventricular myxoma will produce a peripheral embolus.

The present patient had a peripheral embolus, which made the case relatively simple, because examination of the embolus gave the diagnosis. But his history is unusual: he had leg symptoms dating back 2½ years; and one year ago he had an attack similar to the present one. Also note that the attack itself was atypical. The typical presentation of a patient with a peripheral embolus is exemplified in a case reported by Brewin.[2] "A man, age 42, a heavy worker in the timber trade, collapsed at his work at 4 P.M. on December 14 and was taken to the Prince of Wales General Hospital. While lifting timber he had, without warning, a pain in his back and loss of the use of both legs." This is typical of a peripheral embolus, particularly one to the bifurcation of the aorta. It is an acute, sudden, catastrophic, vascular occlusion, not the story of our patient. His atypical picture may be a clue, however.

Looking over the literature, there are reports of myxomas similar to that of the present patient. Young and Hunter[3] reported a 10-year-old girl with a seven-day history beginning with aching in the legs, then vomiting and diarrhea, progressing to anuria and death. At autopsy, they found a myxomatous embolus, which occluded both renal arteries and almost completely occluded the descending aorta. They postulated that the gelatinous tumor originally lodged high in the aorta and partially occluded both the aorta and the mesenteric vessels. Then, because of the gelatinous nature of the tumor, it gradually slid down the aorta under the pressure of the blood and was forced out into the renal vessels while clearing the mesenteric circulation; the vomiting and diarrhea disappeared but anuria developed.

Gerbode[4] reported a patient who had an aortic embolus. No diagnosis of myxoma was made, however. The patient recovered for 20 months before he had another embolus, at which time the diagnosis was made and the myxoma removed successfully. A patient reported by Differding et al.[5] had an eight-month history beginning with hemiplegia, then lightheadedness, then syncope, and finally a saddle embolus. The total course ran a little over eight months with repeated emboli. Thus, the facts that the present patient had symptoms for several years and that his presentation was atypical for thrombotic embolus, are consistent with what has been reported in myxomas.

Physical Examination

Dr. Kay:

Physical abnormalities at the time of admission to Wilford Hall USAF

Hospital were limited to the cardiovascular system. The patient had no neck-vein distention. His carotid pulses were normal. He had decreased pulses in the left posterior tibial and dorsalis pedis arteries. The point of maximum impulse was in the fourth intercostal space at the midclavicular line. The first heart sound was palpable. There were no thrills or lifts noted. S_1 was very loud. S_2 split normally. He had an early diastolic low-pitched *sound,* and an atypical murmur beginning with the second heart sound and of short duration.

Comments

Dr. Schechter:

In Goodwin's review of myxomas,[6] mitral murmurs were very common, mitral insufficiency murmurs being reported in 22 out of 45 cases and mitral stenosis murmurs in 27 out of 45 cases. Early diastolic sounds were frequent, occurring in about 50% of patients. There is bias in this series, however. These figures are based on a survey of practicing cardiologists in England. They apply to myxomas that are diagnosed ante mortem, based on a positive history or physical findings.

Greenwood,[7] in his review based on autopsy cases, presented a somewhat different picture of the physical findings in patients with myxomas, concluding that the typical patient with myxoma shows atypical or difficult-to-hear murmurs. In the present patient the physicians at the hospital at Clark Air Base described a mitral diastolic rumble. When we examined him, he did have a loud S_1 and an early diastolic sound, which could indicate the diagnosis of mitral stenosis. None of us confirmed the presence of murmurs to suggest either mitral stenosis or mitral insufficiency. It is interesting that postoperatively the loud first sound and the diastolic sound both disappeared. The point of the murmur changing with position is frequently made. When you talk of changing murmurs, you must remember that the murmur of mitral stenosis increases with exercise and is sometimes heard better in positions other than supine, i.e., left lateral, left lateral recumbent, leaning forward, or on hands and knees. The fact that a diastolic rumble is heard better in one position than in another does not indicate that it is caused by a myxoma.

Laboratory Studies

Dr. Kay:

An initial CBC showed a white count of 10,800 with a normal differential. The patient had a hemoglobin of 11.8 gm and a hematocrit of 37%. His sedimentation rate uncorrected was 48. BUN, a creatinine, fasting blood sugar, SGOT, SGPT, lactic dehydrogenase, bilirubin, and protein electrophoreses were normal. He was not specifically studied for hemolysis. A lung scan was within normal limits. He was afebrile for the first two days after admission. On the third day, he ran a fever of 102.6° F. Appropriate cultures were taken, but the reason for the fever was never determined. He was afebrile after that and on the eighth day was catheterized.

Comments

Dr. Schechter:

The manifestations of left atrial myxomas can be divided into four broad groups: hemodynamic, hematologic, biochemical, and nonspecific or constitutional. There are two major hemodynamic abnormalities. The first is obstruction of blood flow, most commonly at the mitral orifice. Syncope may be the presenting symptom produced by a tumor obstructing flow and temporarily interrupting cardiac output. Pulmonary congestion may occur as a result of interference with outflow from the left atrium. The second abnormality is embolization as discussed above: single or multiple. Emboli may consist of the entire tumor or small fragments of it.

Hematologic abnormalities are frequent, occurring in approximately 45% of patients.[8] There has been evidence, based mostly on blood smears, that this is due to hemolysis. In one case[9] red cell survival was shown to be shortened. This shortened survival was corrected following removal of the myxoma. It seems reasonable that the hemolysis in patients with myxomas is the same as in patients with intracardiac prosthesis, that is, due to mechanical trauma. Polycythemia has been reported in one patient with a right atrial myxoma,[10] in whom there was polycythemia for several years before the tumor was recognized and removed. The preoperative arterial saturation was 93%. Postoperatively, this improved to 99%, with regression of the polycythemia. It was postulated that this was secondary to multiple small pulmonary emboli with arterial unsaturation.

Biochemical abnormalities have been found in many of these cases. Hyperglobulinemia is the most frequent, occurring in about one third of patients with myxomas. On electrophoresis, the globulins are generally normal, being increased in quantity rather than altered in quality. There has been interest in determining whether these globulins were antibodies, but thus far there has been no conclusive evidence. It has been suggested that there are abnormal mucopolysaccharides released from the myxoma that stimulate antibody formation.

Constitutional findings are frequent in left atrial myxomas; 90% show some type of constitutional manifestation. Fever is the most common, occurring in over 50% of the patients; cachexia is less common, occurring in about 30% of patients, and anorexia or malaise also occurs in about 30%.

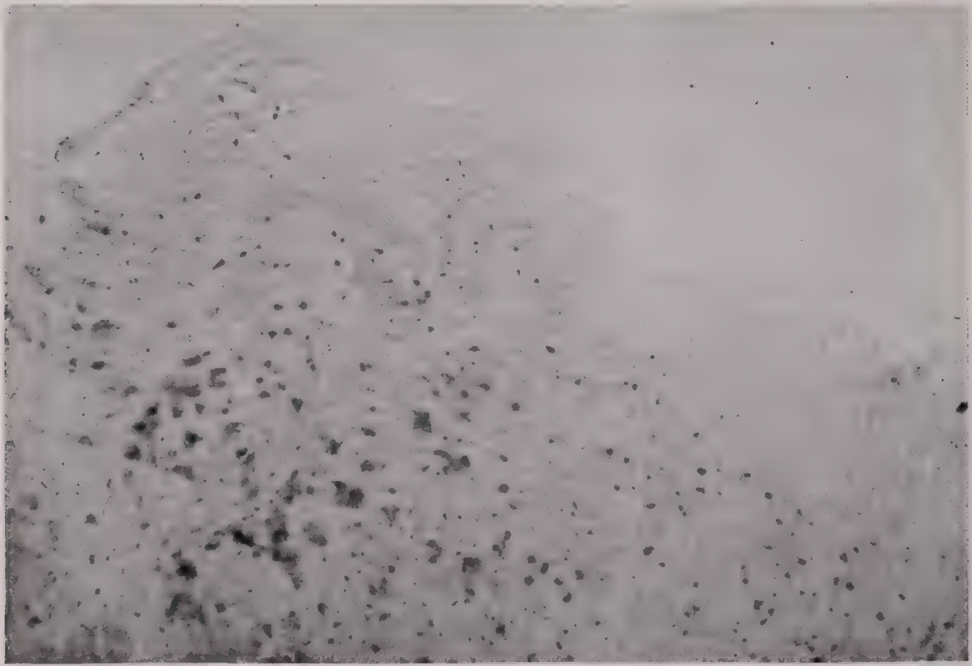

Fig. 1—Photomicrograph of saddle embolus showing a non-stratified structure irregularly flecked with calcium deposits and a loose myxoid background. H. E. original magnification times 25.

Pathologic Findings

Dr. William M. Wahle:*

The first photomicrograph (Figure 1) of the material removed at Clark Air Base represents the saddle embolus; I think you can appreciate that this is not an ordinary blood clot. The outside of the material shows an endothelial lining; furthermore, it is not stratified like a normal clot. It has definite structure composed of a rather nondescript eosinophilic background. Scattered throughout this material are small flecks of calcium which represent areas of dystrophic calcification, and there are numerous small nuclei scattered through the background material. The surgeon astutely recognized that this was not a usual clot and the pathologist at Clark Air Base suggested that this might be coming from a cardiac myxoma because of its characteristic features. The next photograph (Figure 2) represents a magnified view showing an occasional flattened nucleus that lines the outside of this clot. The amorphous ground substance which makes up the bulk of this tumor is noted.

Comments

Dr. Schechter:

This points out one very important lesson: Any time a peripheral embolus is removed, it ought to be examined completely, because very often this is the clue that cinches the diagnosis.

Having had the diagnosis made for us at the time the patient was referred here, one may ask: why catheterize him at all. I think there was a good reason for cardiac catheterization since, at least in some of the cases reported, including two which were autopsied, the embolus consisted of the entire tumor. In one patient who embolized and had the diagnosis made by examina-

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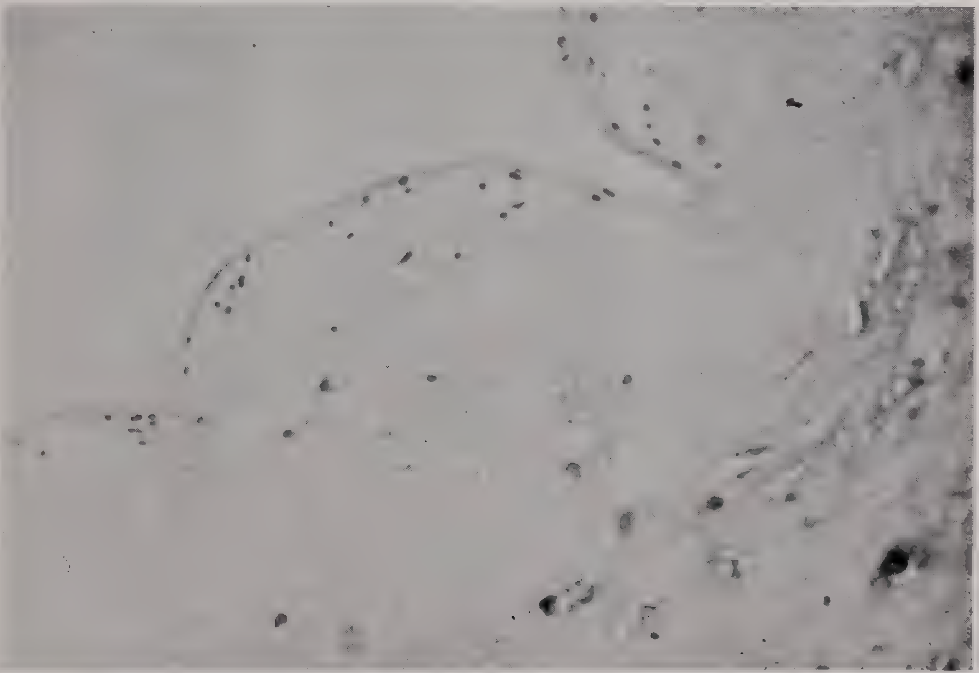

Fig. 2—Photomicrograph of saddle embolus showing an occasional endothelial cell compressed on the luminal side. An amorphous type of ground substance supports the irregularly shaped cells. H. E. original magnification times 100.

tion of the embolus,[11] no filling defects were noted within the heart on angiogram. The surgeons elected not to operate, and for a period of eight months to the time of the report she has done well. Before one submits a patient to open heart surgery, it is wise to make sure there is a lesion. Also it is helpful to know whether you are dealing with an atrial or ventricular tumor. Rare cases of systemic embolization from right atrial tumors and pulmonary embolization from left atrial tumors have been reported.[12] Catheterization is relatively benign compared to the eventual surgery. It is wise to give the surgeon as much information as possible beforehand rather than trust that when he has the chest open on the operating table he will be able to sort out what may be a very confusing picture.

Cardiac Catheterization Data

Dr. Morton Korn:*

The present patient had right-heart and retrograde left-heart catheterization. The arterial catheter was inserted retrograde into the left atrium. Angiography was performed in the left atrium. Figure 3 shows the right anterior oblique view during systole. The globular filling defect in the atrium is unmistakable evidence of a space-occupying lesion—in this case, the myxoma. Figure 4 shows diastole. The filing defects have moved across the plane of the mitral valve. Figures 5 and 6 show systole and diastole in the left anterior oblique projection. Again, the filling defects can be shown.

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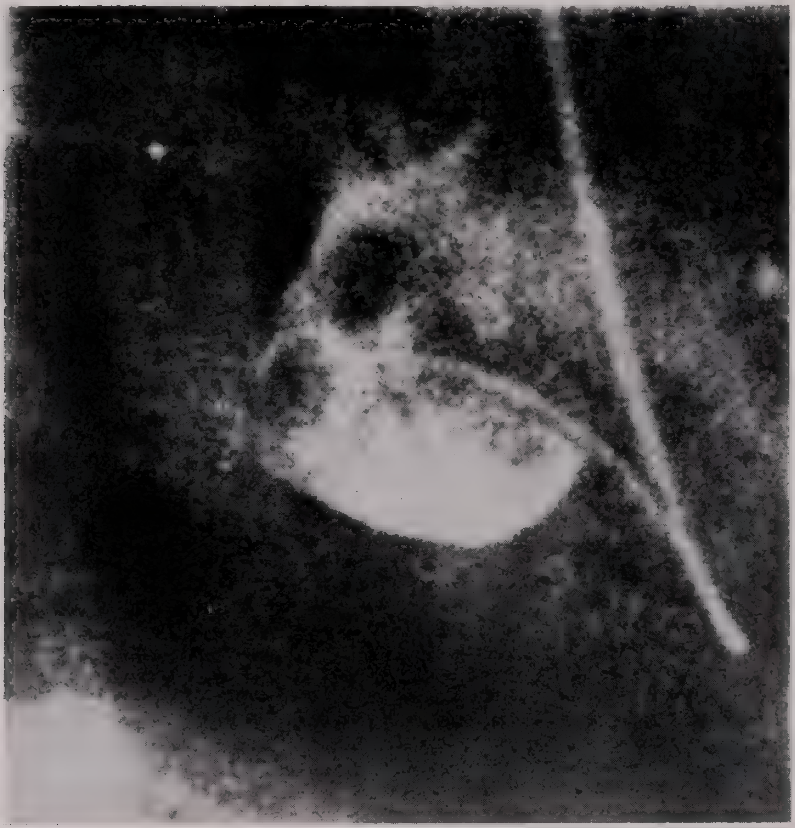

Fig. 3—Left atrial injection. Right anterior oblique view during systole.

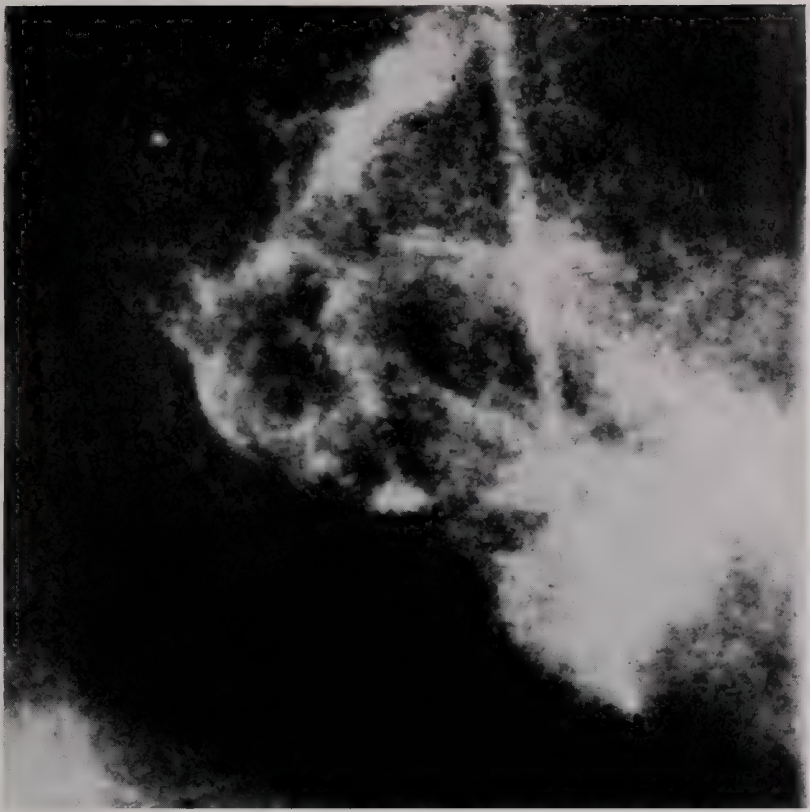

Fig. 4—Left atrial injection. Right anterior oblique view during diastole.

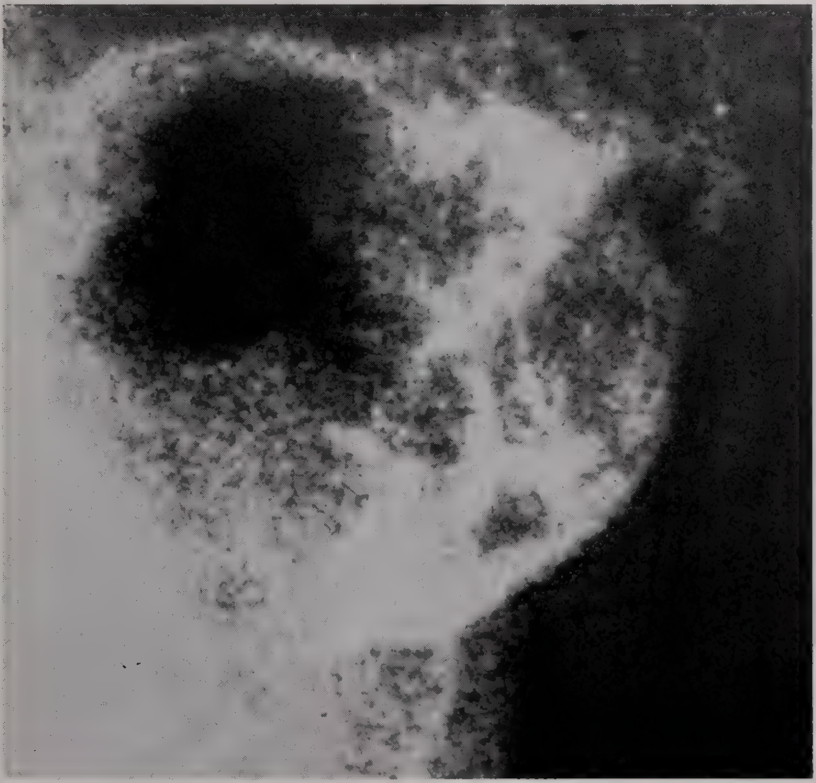

Fig. 5—Left atrial injection. Left anterior oblique view during systole.

The cardiac outputs and intracardiac pressures were normal.

It is possible to get both false-positive and false-negative results in patients with myxomas. The most common problem is a false-positive in which non-opacified dye draining from the pulmonary veins into the left atrium is interpreted as a filling defect. For this reason, it is wise to take several different projections and see whether these filling defects are constant, or seem related to blood draining from the pulmonary veins.

Surgical Findings

Dr. Byron N. Dooley:*

The present patient at surgery was found to have a very large gelatinous mass filling almost the entire left atrium. On palpation of the atrium externally, you could feel a very definite thump against a palpating finger;

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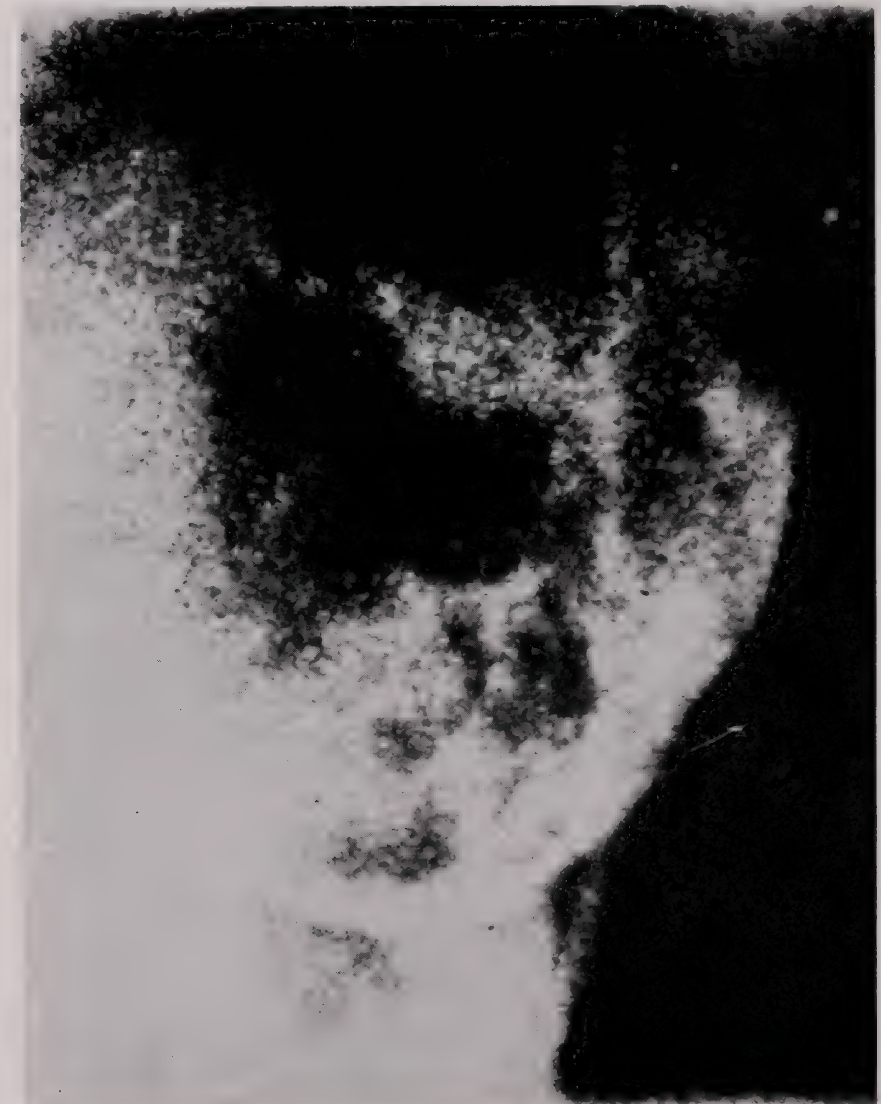

Fig. 6—Left atrial injection. Left anterior oblique view during diastole.

to the surgeons through the years the thump has been one of the warnings that perhaps there was a myxoma present in the left atrium. Prior to the days of open heart surgery, a great many surgeons were caught doing closed mitral valvulotomies, only to their chagrin to find that the left atrium was filled with either clot or tumor. We think that the horse-and-buggy days of open heart surgery and cardiology are all behind us now, and I feel very strongly that diagnostic workup, including cardiac catheterization, is definitely necessary in patients undergoing heart surgery today. It is very difficult when operating on the heart to explore it as you can the abdomen or the chest and know what you are doing both anatomically and physiologically. We feel that we always want to know where things are and what we are dealing with prior to surgery. This tumor was very easily removed under extracorporeal circulation.

The results in general with tumors of the heart have been very good and we feel that a very aggressive approach should be taken to them. We have operated upon six patients with cardiac tumors since 1962. Five of them are alive today and doing quite well. Three of these have been myxomatous tumors. Two of these patients presented with peripheral emboli, as did the present patient. One came in with mitral obstructive symptoms. None of the patients with myxomas has died. The success has been mainly due to extracorporeal circulation. The heart-lung machine that we are currently using at Wilford Hall is the Travenol Disposable Bubble Oxygenator, which is available in the operating room at all times for any thoracic operation. It is quickly set up and is all-disposable. The unit is primed in adults with Ringer's lactate and with no homologous blood. The surgical approach to

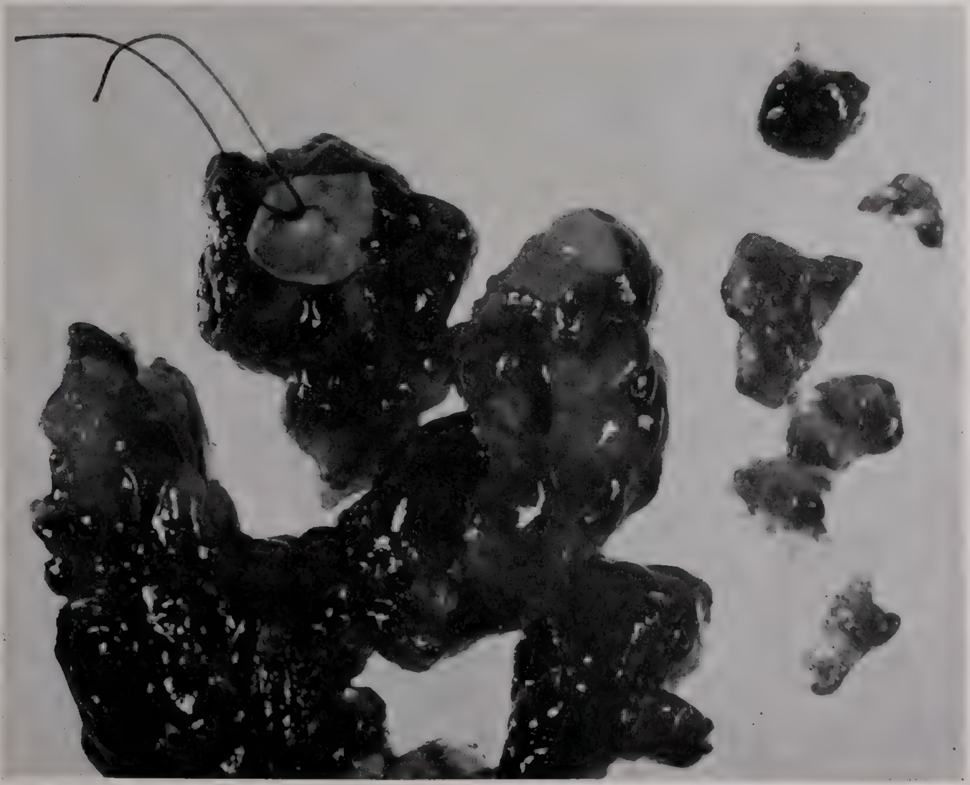

Fig. 7—Gross photograph of the cardiac myxoma. The smaller fragments represent particles that were very loosely attached to the main polypoid tumor.

tumors has been relatively standardized. Since most tumors are myxomas and most are in the atrial chambers, we approach them in a manner similar to that for valve replacements. In the present patient a right thoracotomy was used; by making a left atrial incision we could expose the myxoma inside the left atrium. The tumor was attached by a 1-cm base, and we were able to excise that portion of the atrial septum and resuture it in addition to

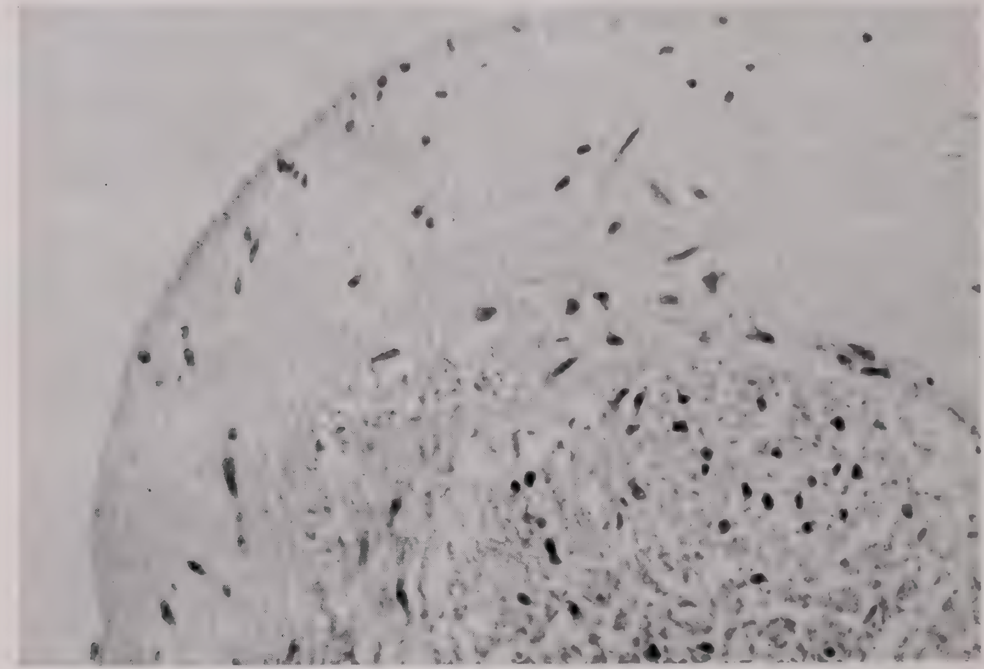

Fig. 8—A section of a normal mitral valve. The loose connective tissue of the subendocardial portion of the valve shows a close similarity to that seen within the tumor. H. E. original magnification times 100.

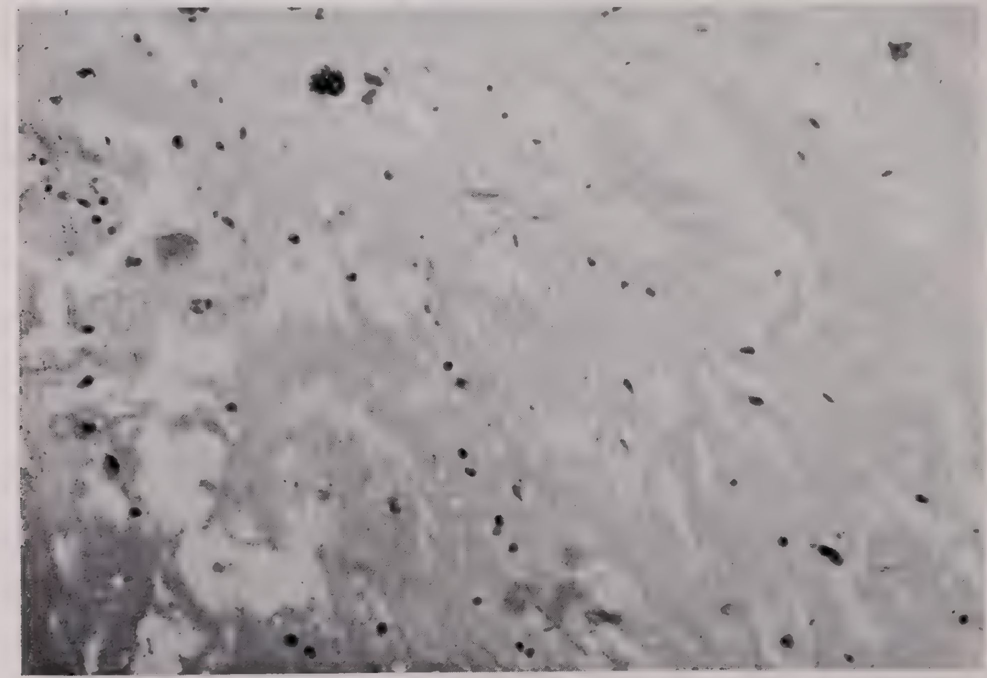

Fig. 9—Photomicrograph of the tumor revealing the loose PAS and Alcian Blue-positive ground substance supporting the irregularly shaped cells. PAS original magnification times 150.

removing all of the tumor.

Pathological Findings

Dr. Wahle:

This is the gross photograph of the tumor removed from the patient (Figure 7). The suture is through the point of attachment. The tumor is supported on a rather thin, delicate stalk. The mass is quite polypoid and friable. Cardiac myxomas are divided grossly into two types. This type, which is usually very jelly-like and loose in consistency, fragments quite easily, giving rise to emboli. The second type is a more globoid round structure that usually has no papillations, is firmer and, therefore, does not readily give rise to emboli. This photograph (Figure 8) shows the myocardial fibers and the subendocardial tissue of a normal mitral valve.

I want to draw your attention to the loose ground substance in this normal valve, as I think we can see the same thing in the tumor. Notice the small stellate cells scattered throughout the normal subendocardial portion of the mitral valve. This is a high-power view of the tumor (Figure 9) showing the amorphous ground substance and the irregularly shaped cells scattered throughout the background. At times the cells appear to be forming small blood vessels and, in fact, many authors and authorities believe that these cells are actually modified endothelioid cells rather than fibroblasts. A periodic acid Schiff stain performed on this tumor suggests that the ground substance is a mucopolysaccharide rather than fibrin or elements of blood clot. A modified Alcian Blue stain, done at pH 3.4, shows unstained material in the midst of Alcian Blue-positive mucopolysaccharide. The unstained material has the characteristics of fibrin.

Conclusion

Dr. Schechter:

Left atrial myxomas are certainly the most common of the primary cardiac tumors. Fortunately, myxomas are also the tumors most amenable to surgical cure. For this reason, it behooves each of us to keep in mind the features of myxomas as discussed today. Even if you see only one patient with a myxoma in your practice, that should be a cure.

Eliot Schechter, Lt. Colonel, USAF, MC*
Chief, Cardiology Service

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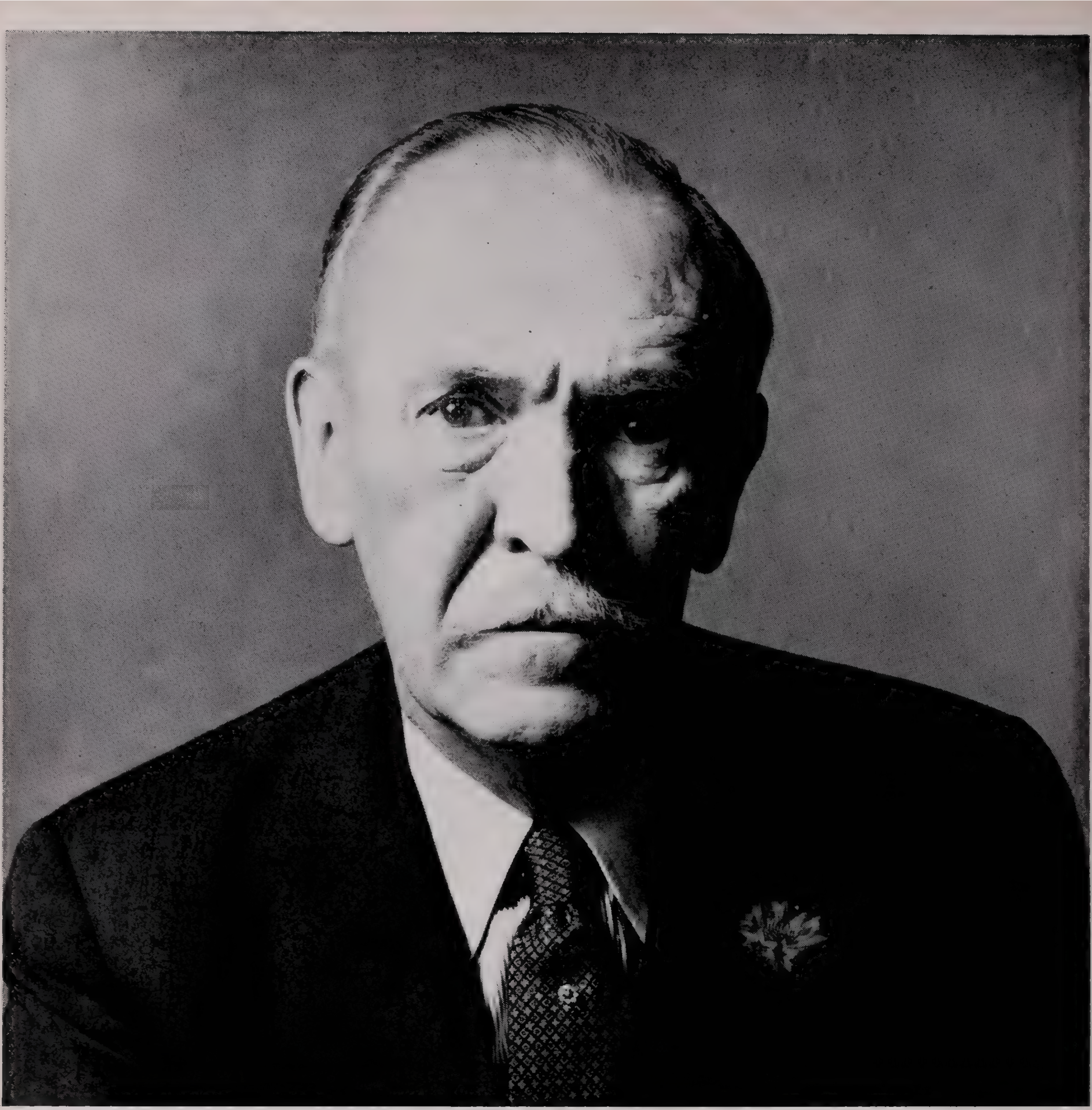
7-12. May be secured from the author or the reprints.

If children grew up according to early indications, we should have nothing but geniuses.—Goethe



Help the Needy!

This patient may appear to "have everything" but, like so many people getting along in years, he may well be in need—*medically.* Though there is no evidence of organic disease, he does have symptoms (fatigue, vague aches and pains, malaise) that may be indicative of—

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Thiamine HCl	—	5.0 mg.
Thiamine mononitrate	10.0 mg.	—
Riboflavin	5.0 mg.	—
Niacinamide	50.0 mg.	—
Pyridoxine HCl	3.0 mg.	—
Calcium pantothenate	20.0 mg.	—
Ferrous sulfate exsic.	30.0 mg.	—
Ascorbic acid	100.0 mg.	—
		Contains 15% alcohol†

† Some Loss Unavoidable.

Contraindication: Carcinoma of the prostate, due to methyltestosterone component.

Warning: Some patients with pernicious anemia may not respond to treatment with the Tablets or Capsules, nor is cessation of response predictable. Periodic examinations and laboratory studies of pernicious anemia patients are essential and recommended.

Side Effects: In addition to withdrawal bleeding, breast tenderness or hirsutism may occur.

Suggested Dosages: *Male and female*—1 Tablet or Capsule, or 3 teaspoonfuls Liquid, daily or as required.

In the female: To avoid continuous stimulation of breast and uterus, cyclic therapy is recommended (3 week regimen with 1 week rest period—Withdrawal bleeding may occur during this 1 week rest period).
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Symbols in a life of
psychic tension

B.A.
cum laude

V.P.
at thirty-two

ECG
and complete
examination normal
(persistent palpitations)

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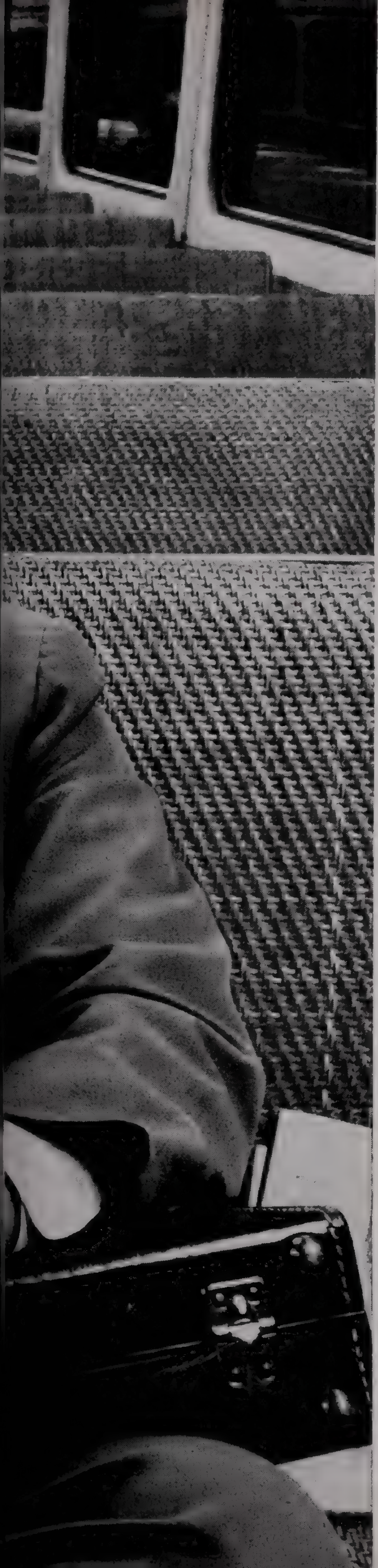

Rx

Valium® (diazepam) *t.i.d.* and *h.s.*

B.A. (*cum laude*)...V.P. (at thirty-two)...symbols that illuminate the quality of a life...the satisfactions of achievement, as well as its price...the pressures and stresses that can often create cardiac manifestations of psychic tension. For this kind of patient—with no demonstrable pathology—consider the singular benefits of Valium (diazepam).

With its pronounced calming action, Valium can relieve psychic tension promptly, attenuating its somatic signs and symptoms. Further, Valium is distinctly useful when somatic and depressive symptomatology (secondary to psychic tension) coexist. And Valium is generally well tolerated; in proper maintenance dosage, it seldom dulls the senses or interferes with functioning.

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Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms have occurred following abrupt discontinuance. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation, have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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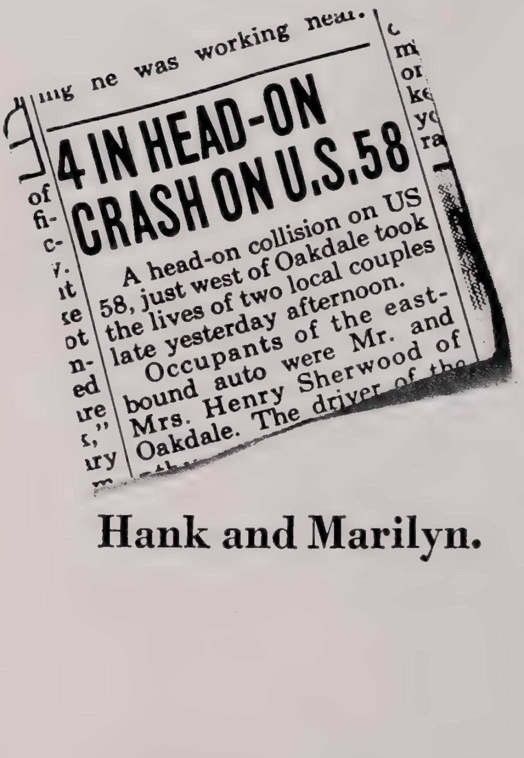
to help relieve psychic tension
and its somatic symptoms

Guess who Syd and Gladys ran into the other day?



ne was working near.

4 IN HEAD-ON CRASH ON U.S. 58

A head-on collision on US 58, just west of Oakdale took the lives of two local couples late yesterday afternoon.

Occupants of the east-bound auto were Mr. and Mrs. Henry Sherwood of Oakdale. The driver of the

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Your best chance to head off a "head-on" is to think negatively. Assume that behind every oncoming truck or car there's a good guy about to make a bad mistake. And, be prepared to get out of his way if he does.

Whenever, wherever you drive . . . drive defensively. Watch out for the other guy. It's the best way there is to watch out for *you*.

Watch out for the Other Guy.

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Pediatrics

The Battered Child Syndrome

Part IV—Summary

REALIZATION THAT CHILD abuse does exist and recognition of the subtleties of the less-than-obvious case are important in protecting the abused child against further trauma or even death. Some of the major alerting findings include: a history of previous trauma; lesions (burns, fractures, bruises, etc.) in different stages of healing; evidences of injury disproportionate with the history given; and the lack of appearance of new lesions following removal of the child to a new environment.

The incidence is unknown, but in one survey 10% of all children seen in an Emergency Room for trauma were found to be victims of child abuse. If this is anything near the true incidence, then there are many more cases than are being recognized or reported.

There can be a large variation in abuse ranging from withholding feedings, emotional neglect, and over-zealous spanking, to homicide. The spectrum is very broad, and those patients actually presented for care represent only the "iceberg effect" with a greater number being unseen.

Repeated trauma occurs in 30 to 50% of the children and the *death rate is 10%.* This emphasizes the importance of recognizing and reporting, and the institution of appropriate protective measures for these patients.

Potentially, anyone can abuse a child. The abuser can come from any walk of life, socio-economic group, race, or educational level. He has a low frustration level and is usually impulsive. Some are overtly psychotic, often classified as having character disorders; but by no means is this always the case. Many are purported to have been beaten themselves. While being interviewed they often display little affect. Often one or both parents or the guardians are the assailants, and one may "cover" for the other while being interviewed.

Minnesota passed the beginnings of a reporting law in 1963 which, as amended in 1965 and 1967, stands today. All health personnel who suspect a case of child abuse are required by law to report such a case under penalty of law (three months and/or $100.00 maximum penalty) for not reporting. This law was suggested and revised under impetus from the Minnesota State Medical Association and the Minnesota Department of Public Welfare. A case is reported first by telephone and later by written statement including names, addresses, extent and type of injury, history obtained, and other pertinent data such as x-rays (skulls, long bones), etc. These reports are made to the police and welfare departments. They then investigate the reports and dispose of the cases appropriately. The person who makes the report is *not* liable and medical privilege is waived. When court proceedings are necessary, the greatest emphasis is on the protection of the child instead of punishment of the assailant; and cooperation of the physician is of great importance. If a specific law (murder, assault, etc.) has been broken, then appropriate action against the assailant will be taken.

Because of increasing awareness of the syndrome and the reporting law, more cases are being reported annually. It is seriously doubted that the actual incidence of abuse is changing.

The authors suggest that the state law be amended to permit any person to report a suspected battered child without fear of liability, if such report is given in good faith. We also suggest that Minnesota establish a central reporting agency where known and suspected cases can be filed so that, if a case appears in an Emergency Room or physician's office, it can be promptly determined if that patient has previously been reported to be a battered child. Such an approach may help to identify those who use different facilities each time the child is battered and permit prompt application of protective services to that patient.

Hugh D. Allen, M.D.*
Robert W. ten Bensel, M.D.†
Richard B. Raile, M.D.‡
Minneapolis, Minnesota

From the Department of Pediatrics, University of Minnesota Medical School.

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‡Professor in Pediatrics, University of Minnesota and Chief of Pediatrics, Hennepin County General Hospital.

John Hunter's Menagerie

Before going off to war, John made plans to start a menagerie for the study of all kinds of animals. He had leased two acres in Earl's Court in the village of Kensington where he proposed to build a house for his collection.

The design of the house was as unique as the idea of the menagerie was unorthodox. Over the door hung the head of a crocodile with gaping jaws. Four life-size statues of lions, two rearing and two crouching, were set on each side of the building. Back of the house was a den where real lions and leopards were chained. Over the den there was a mound of earth, topped with piles of seashells; in the shape of a little fort on which was mounted a small gun.

The strangest sight was the barnyard. Here all kinds of domestic and wild animals roamed in confusion. Rare birds and serpents, ostriches, geese, and pheasants mingled with buffalo and deer. Fowl and human teeth grafted on the combs, hens with roosters' feathers, goats and dogs were all there for some type of experiment. In a small fishpond Hunter bred eels, leechs, carp, and river mussels. Hedgehogs and other hibernating animals were kept in burrows to yield their secrets of winter sleep. No specimen was too bizarre for the surgeon-scientist to scrutinize. There were goose eggs for the study of embryology, pond water for fresh-water life, the skeleton of a giant dancing bear contracted for with a traveling gypsy when it was alive.

He frequented the pet shops, looking for strange creatures, and begged zoo keepers and members of expeditions for any rare beasts they might encounter. Dead animals were useful too. Certain parts he pickled in jars, others he dried. The rest were boiled down in a copper vat and the skeletons preserved.*

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*Sarah R. Riedman: Masters of the Scalpel, 1962.

Advice from a Medieval Physician

And of those things which are incumbent on the student of this Art (Medicine) are that he should constantly attend the hospitals and sick-houses; pay unremitting attention to the conditions and circumstances of their inmates, in company with the most acute professors of Medicine; and enquire frequently as to the state of the patients and the symptoms apparent in them, bearing in mind what he has read about these variations, and what they indicate of good or evil. If he does this, he will reach a high degree in this Art. Therefore it behooves him who desires to be an accomplished physician to follow closely these injunctions, to form his character in accordance with what we have mentioned therein, and not to neglect them. If he does this, his treatment of the sick will be successful; people will have confidence in him and be favourably disposed towards him, and he will win their affection and respect and a good reputation; nor withal will he lack profit and advantage from them. And God Most High knoweth best.*

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*Ali ibnu 'l-Abbas, Persian physician.

History of Medicine

Wilford Hall USAF Hospital

Wilford Hall USAF Hospital is a modern 1,000-bed general hospital, consisting of one 500-bed unit put into operation in 1957 and a second unit completed in December 1960. This nine-story hospital is the largest single structure of its kind in the Department of Defense. Only an extremely farsighted person could have predicted in 1942 that from the newly opened hospital adjacent to Kelly Field would come this giant of the United States Air Force Medical Service.

Wilford Hall USAF Hospital traces its ancestry back to June 15, 1941, when the first shovel bit into the clay-like San Antonio earth and broke ground for the Station Hospital, a unit of the San Antonio Aviation Cadet Center. Officially opened on June 8, 1942, the facility offered the usual services and included a fully equipped dental clinic. A secondary mission consisted of the conduct of a limited training program for selected medical officers from the School of Aviation Medicine and the operation of a Medical Training Center School for enlisted men.

By 1943 the hospital had expanded to 1,200 beds, and its principal functions were the medical processing of aircrew candidates and aviation cadets, corrective surgery on aircrew candidates, and operation of a School of Aviation Medicine branch.

On February 1, 1946, the Station Hospital became the Army Air Forces Regional and Convalescent Hospital. In mid-June 1950 the hospital was redesignated a United States Air Force Infirmary. This status was short-lived, however, for soon thereafter redesignation instructions were received from the Secretary of Defense to reopen the facility as a 100-bed hospital.

Cancellation of the infirmary status was accidentally prophetic, for a military incident put the hospital back on a fully operational basis; the North Koreans had invaded South Korea. Six weeks after the start of hostilities, the medical group (designated the 3700th Medical Group at that time) was authorized to set up a 475-bed hospital, which became known as the 3700th USAF Hospital. On December 11, 1950, Lackland Air Force Base was designated a major port of debarkation for American military men returning from Korea. The hospital, which had been providing temporary treatment for Korean War casualties, was ordered to increase its capacity to 1,000 beds, including 500 beds allocated for wounded servicemen.

Construction of the present facility began on October 11, 1954, and was completed in mid-1957. Patients were transferred to the new building during the latter part of September, and the official dedication was held on November 16, 1957. The new facility opened with 500 beds, but it was built on a 1,000-bed chassis. When the Aerospace Medical Center was established at Brooks Air Force Base, Texas, in October 1959, the hospital and the School of Aviation Medicine became two of its components. This Center was the first Air Force medical organization to provide comprehensive facilities for clinical therapy, research, and education. In 1960 completion of the teaching wing added another 500 beds and classroom space for the training of residents, interns, nurses, and medical technicians.

The following year Wilford Hall USAF Hospital was selected to aid the nation's space program when the National Aeronautics and Space Administration (NASA) requested clinical medical support for the first suborbital space flights of Project Mercury. Medical personnel were made available for the entire Mercury series of space probes. In 1961, also, the Aerospace Medical Division was created in order to provide medical support to the rapidly expanding field of aerospace development and operations in the United States. Wilford Hall USAF Hospital and the other units that formerly constituted the Aerospace Medical Center were absorbed by the new unit on November 1, 1961. The Division was established as part of the Air Force Systems Command.

Significant achievements were made in many areas. The open heart surgery program, begun in 1962, advanced through countless refinements. The team approach, together with standardization of techniques and simplified equipment, made it possible to operate successfully on complex cardiac conditions, including multiple valve replacements. Wilford Hall USAF Hospital, being the only Air Force cardiac surgical center, began to perform routinely three or four cardiac procedures a week. This program continues to be important.

On March 2, 1963, the hospital was named for Major General Wilford F. Hall, a former surgeon of the Air Materiel Command, a distinguished flight surgeon, and a recognized clinical specialist. General Hall, who died in 1962, made numerous contributions to the Air Force Medical Service. Renaming the hospital for a deceased officer changed the Air Force custom of giving each medical facility a numerical designation or the name of the installation on which it was located. Commensurate with advances in medicine, the hospital continued to increase its capabilities. The MacKown Dental Clinic was added to the growing complex in June 1965. Replacing six dispersed dental units on Lackland Air Force Base, this modern clinic consisted of treatment rooms, a library, classrooms, laboratories, a conference room and other facilities.

The United States Air Force Central Eye Bank was established in 1965, and by the middle of 1966 it was in full operation, supplying military and civilian hospitals with fresh or preserved eye tissue. On December 15, 1967, an agreement was signed between the University of Texas Medical School at San Antonio and Wilford Hall USAF Hospital to permit the interchange of the medical staff of both institutions as consultants and teachers, of interns and resident physicians for training purposes, and of the research staff; the establishment of cooperative research studies; and the teaching of medical students.

In 1967 the United States Air Force Central Tumor Registry was established at Wilford Hall USAF Hospital in order to have all tumors that were diagnosed in Air Force medical facilities registered at one institution, no matter where the Air Force personnel might have moved. Records of therapy, complications

TABLE 1

Clinical Workload, Wilford Hall USAF Hospital (FY 1967)

	Per Year
Admissions	20,136
Average daily occupied beds	869
Births	1,584
Outpatient visits	696,820
X-ray examinations	133,573
X-ray films exposed	281,376
Laboratory procedures	1,753,171
Major surgery	8,458
Dental clinic procedures	677,100
Dental laboratory procedures	314,844
Physical therapy treatments	192,292
Occupational therapy treatments	77,467
Autopsies	224

TABLE 2

Training Programs Offered at Wilford Hall USAF Hospital

	Date Established	Years of Approved Training	Number Per Year
Internships			
Types 0, 1, 2, 3, 4		1	28
Types 5, 6, 7, 8		1	6
Straight medicine		1	6
Straight surgery		1	4
Residencies			
Anesthesiology	1954	2	6
General surgery	1957	5	3
Internal medicine	1957	3	7
Neurological surgery	1965	5	1
Obstetrics and gynecology	1959	4	2
Ophthalmology	1968	3	2
Orthopaedic surgery	1955	4	4
Pathology	1958	4	2
Pediatrics	1958	2	4
Psychiatry	1964	3	3
Radiology	1957	3	4
Thoracic surgery	1962	2	2
Urology	1959	4	2
Fellowships			
Allergy	1964	2	1
Cardiology	1964	1	1
Gastroenterology	1966	1	1
Hematology	1964	1	1
Infectious disease	1964	1	1
Pediatric allergy	1964	2	1
Pulmonary disease	1964	1	1
Renal disease	1964	1	1
Endocrinology	1966	1	1

and progress were established for all known patients and provisions made for adding new ones as they were identified.

Present Operation

Since 1957 Wilford Hall USAF Hospital has been characterized by steady growth in the number of patients treated, personnel assigned, workload capacity, research projects, and educational programs. The hospital furnishes full-scale medical care not only to the military population, dependents, and retired personnel in the San Antonio area, but also to patients with complex diagnostic and treatment problems referred from Air Force installations all over the world. It has three closely related missions: (1) patient care, (2) medical education, and (3) clinical research. A tremendous wealth of clinical material is available to the interns, residents and teaching staff. Table 1 indicates the workload for the most recent representative year (1 July 1966 to 30 June 1967).

Recognized as the leading medical center of the United States Air Force, the hospital has a large, competent staff that includes many members who are recognized nationally in their particular specialty. The present staff consists of:

Physicians	122
Dentists	53
Administrative and allied services	94
Airmen	1,368
Nurses	
Military	262
Civilian	57
Other civilian employees	474
Red Cross	18
Red Cross volunteers	85

All postgraduate training is under the supervision of diplomates of the various specialty boards, and all teaching programs are fully approved by the Department of Graduate Medical Education of the American Medical Association and the appropriate specialty boards. Table 2 shows the internships, residency programs and fellowships that are offered at Wilford Hall USAF Hospital.

Physicians of Wilford Hall USAF Hospital take an active interest in the welfare of San Antonio citizens by serving as consultants to Santa Rosa Medical Center, Robert B. Green Hospital, and the San Antonio State Tuberculosis Hospital. They also serve as visiting professors to six universities. The University of Texas Dental Branch at Houston is also affiliated with Wilford Hall USAF Hospital for teaching purposes. The civilian consultant program provides the hospital with the services of 121 civilian consultants, including 72 professors at university medical schools throughout the United States.

Wilford Hall USAF Hospital has a clinical research laboratory that is engaged in human research studies as well as animal studies. The main function of this laboratory is to support the research interests of the teaching and resident staff. During the past year, many members of the staff have presented papers at local, state, and national scientific and technical meetings and have been authors of papers published in various medical journals. As a result of the excellent reputation of the hospital, the patient population has continued to increase. Therefore, plans for updating and increasing the number of operating rooms, outpatient clinics, and educational and research facilities already exist; these planned improvements are scheduled to begin in 1969. After completion of this construction program, it is anticipated that Wilford Hall USAF Hospital will continue to maintain the reputation for excellence in patient care, medical education and clinical research established during earlier years.

Thomas H. Crouch, Major General, USAF, MC*
Robert E. Smith, Colonel, USAF, MC†

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*Commander, Wilford Hall USAF Hospital, 1 June 1965 to 1 November 1968. Present address: Director of Professional Services (AFMSP), Office of Surgeon General USAF, Washington, D. C. 20333.

†Director, Education.

Old men delight in giving good advice as a consolation for the fact that they can no longer set bad examples.—La Rochefoucauld

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The reputation of a man is like his shadow,—gigantic when it precedes him, and pygmy in its proportions when it follows.—Tallyrand

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GENERAL SURGEON interested in some general practice to associate with a 2-man partnership in a rich agricultural community in southern Minnesota. Modern hospital and new clinic building. Hunting, 9-hole golf course, swimming pool. Salary open and full partnership as soon as desired. Write: MINNESOTA MEDICINE—405, 375 Jackson, St. Paul 55101.

INTERNIST AND GENERAL PRACTITIONER wanted to join a five-man clinic group in Minneapolis. Complete laboratory and X-ray with board roentgenologist. Excellent hospital staff associations. Salary arrangement to start with, early partnership. Write MINNESOTA MEDICINE—289; 375 Jackson, St. Paul, 55101.

Continued to page 548

Abstracts, Briefs and Commentaries

PENETRATING WOUNDS OF THE HEART
AN ANALYSIS OF 459 CASES

Both the non-operative and operative methods for treatment of penetrating wounds of the heart have been proposed by numerous authors over the past 30 years. The present article summarizes the experience with 459 penetrating wounds of the heart, at Parkland Memorial Hospital during a nine-year period. Of the 373 who were dead on arrival, 80% had been injured by gunshot; in contrast, only half of the 86 patients admitted alive had been injured in this manner. The mortality rate for the seven years prior to 1966 was 36%, the cause of death in over half of these cases being attributed to recurrent cardiac tamponade.

Beginning in 1966, all cases of penetrating wounds of the heart were treated primarily by open thoracotomy methods with a significant reduction in mortality rate from penetrating stab wounds, but no significant reduction in wounds produced by gunshot. There was a striking contrast between the 43% mortality figure with pericardiocentesis therapy alone and the 16% mortality rate when open thoracotomy was performed. From autopsy data on the patients arriving dead at the hospital, the authors noted the left ventricle was involved in over half of the cases, but in only 3% of surviving patients. Interestingly, patients with injuries of only the left atrium survived; but three of seven patients with right atrial injuries succumbed in the hospital.

This report generated comments from five members of the audience, most of whom agreed that the more aggressive open thoracotomy approach to both stab wounds and gunshot wounds of the heart was indicated. It was also pointed out that the pump oxygenator was needed on standby to salvage those cases which had previously been irreparable.

Evan F. Lindberg, Lt. Colonel, USAF, MC
Surgeon, Thoracic Surgery Service

Sugg, W. L., Roa, W. J., Ecker, R. R., Webb, W. R., Rose, E. F., and Shaw, R. R.: J Thorac Cardiov Surg 56:531, 1968.

SCAR CANCER OF THE LUNG

The authors discuss 20 operative cases of carcinoma developing in scars of the lung. The sex incidence was equal and the average age was 57 years. Seventeen cases were of the bronchiolo-alveolar type, which is the most common variety reported in similar series; one was anaplastic carcinoma and two were squamous cell carcinoma. The cause of the scar was determined in only eight of the cases, the remainder showing marked interstitial fibrosis of unknown etiology. Specific causes of the scar included tuberculosis in five, foreign body in one, infarct in one and bronchiectasis in one. Surgical treatment included either lobectomy or segmental resection. Hilar lymph nodes were involved in only five cases. Of the 16 cases followed for five years, eight remained free from disease.

The pathogenesis of carcinoma developing in pulmonary scar remains unknown, although invariably the carcinomas are associated with a predominantly interstitial type of fibrosis in which degenerative alveolar epithelial hyperplasia has occurred. From the standpoint of x-ray diagnosis, the authors point out that the presence of calcification is of no significance, since it may have been present in the pre-malignant scar. They also question the conclusion drawn in reports dealing with lung cancers of assumed long standing. Rather than an earlier film showing early signs of cancer, they suggest that such cases might, instead, represent pulmonary scars which later develop carcinomatous change.

The conclusion is drawn that these tumors tend to progress slowly and metastasize late and that scar cancers, in general, offer a much better prognosis than bronchogenic carcinoma of the usual type.

Raymond G. Armstrong, Lt. Colonel, USAF, MC
Chief Resident, Thoracic Surgery Service

Ripstein, C. B., Spain, D. M., and Bluth, I.: J Thorac Cardiov Surg 56:362, 1968.

EXPERIENCE WITH AN IMPLANTABLE SYNCHRONOUS PACEMAKER IN CHILDREN

This article deals with five completely implantable synchronous pacemakers in children whose ages ranged from three to 15 years. The etiology of the heart block was surgical in four cases and unknown in one.

The authors recommend the use of an implantable synchronous pacemaker in childhood for persisting postsurgical heart block of at least three to four weeks' duration, regardless of symptoms, and also in the symptomatic child with congenital complete heart block.

It is the authors' opinion that synchronous pacemakers are superior because of their ability to increase cardiac rate in response to the patient's activity, assuring a more normal cardiac function. The ability of the synchronous pacemaker to function as a standby unit if normal sinus rhythm returns is an additional benefit and prevents the bizarre rhythms of pacemaker competition. A further advantage of the synchronous pacemaker is that with battery depletion, the unit converts to a fixed rate, thus preventing recurrent complete heart block, as may occur with battery exhaustion in fixed rate units.

One of the problems which arise in treating heart block in children is the finding of a satisfactory site in which to implant the pacemaker unit, since all of the presently available instruments are relatively large.

Five sites were utilized in this series. When the left posterior, inferior intrathoracic space was used, replacement was somewhat more difficult and required general anesthesia. For this approach, a new thoracotomy incision was made directly over the unit without entry into the free pleural space, since a firm fibrous pocket had developed about the instrument. The unit has been replaced twice in this position.

Another approach also involved a left thoracotomy; but, in order to facilitate replacement, the diaphragm was separated from the costal arch at the posterolateral margin. In this case, the pocket was fashioned extrapleurally with displacement of the spleen anteriorly and the kidney somewhat medially. This extrapleural, retroperitoneal position was somewhat easier to re-enter than the foregoing with incision through the bed of the 12th rib.

A third method involved creation of a retroperitoneal pocket adjacent to the left ileum through a transverse incision made over the iliac crest. This site proved very protective to the unit with less danger of skin breakdown than might occur when the instrument is placed in a subcutaneous position.

Alternative standard methods included subcutaneous implantation on the anterior abdominal wall, which is quite satisfactory in adults and older children; and anterior chest wall placement beneath the pectoralis major muscle. However, the latter approach produced an unsightly bulge as well as atrophy of the overlying tissue.

Larry J. Fontenelle, Major, USAF, MC
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Lindsmith, G. G., Stiles, Q. R., Meyer, B. W., Jones, J. C., Stanton, R. E.: Ann Thorac Surg 6:358, 1968.

Paleolithic Man's Endurance Test

Primitive man was close to nature, but the fallacy of his medicine was its interference with nature. He regarded health and disease as a constant conflict between good spirits and bad spirits, each battling for victory.

The sick person was thus denied rest and quiet, for the disease-demons must be allowed no peace: they must be frightened away by terrifying masks and grimaces; by strange howls, noises, dances; they must be made uncomfortable by beating, biting, pinching, kicking, strangling their host; they must be smoked out by unbearable smells and fumigations. If they were strong enough to endure all this, then by sorcery they must be lured elsewhere, to take their abode in some scapegoat—an animal, or the patient's enemy, or an inanimate object. If they were too clever to be fooled, then they must be appeased with sacrifices and precious gifts. The medicine-man's treatment was so heroic that often he looked as ill and gaunt as his patient, but he never gave up. Even when the struggles of the patient ceased and the soul left his body, the medicine-man would try to blow it back through the various orifices—the mouth, the ear, the anus. Many patients died in their prime, but this merely meant that the demons had conquered—perhaps the deceased had been disrespectful. On the other hand, the medicine-man had many remarkable cures to his credit, and if he kept testimonials, his medicine-bag must have been full of them. In primitive medicine, as in modern, the patient's faith and the physician's personality are important factors in the cure, and often both are the victims of ignorance and suggestion.*

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*Victor Robinson: The Story of Medicine, 1931.

Derivatively Speaking

Arachnoid—from Greek *arachne* (spider's web) plus *oid* (like)

Continued from Page 544.

WANTED: Young physician for association leading to partnership with four well established General Practitioners in fast growing suburb of St. Paul. Excellent clinic facilities in nearly new, partnership owned, well equipped, medical center building. Write: Minnesota Medicine-421, 375 Jackson, St. Paul 55101.

WANTED. General practitioner wanted to join three-man group in a fast-growing area just 30 minutes south of the Twin Cities. You will practice in a new clinic, hospital and nursing home. A complete resume of facilities, practice and area is available. Contact M. H. Hunter, M.D., River's Edge Medical Clinic, Farmington, Minnesota. Telephone 612-463-7181.

OXBORO MEDICAL CLINIC BUILDING (only) for sale in Bloomington, Minnesota's third largest city. Earn attractive return while current lease expires in four years. Clinic comfortably houses 11 doctors, each with 3½ examination rooms. Central air conditioning, adequate parking, and much more. Contact Towle Real Estate Co., 333-2445, Area Code 612. James R. Bingham.

DIRECTOR OF HOUSE SERVICE—An ideal position for someone in family practice who wants a less strenuous life in a stimulating medical environment. Excellent annual fee, plus fringe benefits. Located in Minneapolis, known nationally as an ideal city for family living. Every possible professional, educational, cultural and recreational opportunity. Teams in all major league sports. Write of your interest and come for an expense-paid visit. Write: Minnesota Medicine-422, 375 Jackson, St. Paul 55101.

OB-GYN—Join group of 4 GP's. Immediate work load. Time off assured. Early partnership opportunity. Well equipped clinic, established in 1962, recently expanded, in growing community of 7,000, 30 minutes from downtown Minneapolis-St. Paul. Fully accredited 116 bed. hospital in community. Call or write J. E. Ponterio, M.D. (612) 445-1305. Shakopee Medical Center, Shakopee, Minnesota.

GENERAL SURGEON, board certified or eligible wanted for 5 man group practice community sponsored prepayment plan in Northeastern Minnesota area of 14,000 located on Lake Superior 20 miles from Duluth. Anesthesia by physicians. No general practice. Accredited hospital with radiologist and pathologist services next door to modern clinic. Good schools with swimming pool and indoor ice arena, golf, hunting, fishing. Liberal salary, full partnership 6 months. Write Medical Director, Community Clinic, Two Harbors, Minnesota.

CANOE TRIPS—Complete relaxation in the Quetico-Superior Wilderness. Cruise, fish and explore, or base camp on remote lakes. Paddle, motor or fly in. Bring your family—return home completely rested. Cost only $9.00 per diem, $7.00 under 12. Write: Bill Rom, Dept. MM, Canoe Country Outfitters, Ely, Minnesota.

GENERAL PRACTITIONER urgently needed with two man partnership in Northern Minnesota County Seat Community has modern accredited hospital, stable industry, fine schools and excellent hunting and fishing. Contact Administrator, Roseau Area Hospital, Roseau, Minnesota. Telephone No. 218-463-2500.

MEDICAL ILLUSTRATOR—M.G.H. graduate, worked in hospital, medical school; experienced in surgical drawings, book illustrations, charts and teaching aids. Will work in my Edina home. 941-4499.

BURNSVILLE, NEAR Hwy. # 13 & 35 W. spacious suite in new office bldg., partitioned for medical offices. Over 500 or 1000 sq. ft. Doctors urgently needed for this area. Reasonable rent. Tel. 454-1233.

EXCELLENT OPPORTUNITY for one or two general practitioners. Deer River, Minnesota will be needing one or possibly two physicians by June 1, 1969. The present partnership has an extremely busy practice with higher than average income. An equipped ten room clinic in the hospital is available. For further information contact David McClure, Administrator, Community Memorial, Deer River, Minn. Call collect (218)-246-8245 weekdays or 246-8274 evenings or weekends.

WANTED: Young General Practitioner to join 5 man general practice group. Services of General Surgeon and Radiologist immediately available. College town serving population of 22,000, 30 miles from Twin Cities. Contact Roland M. Hammer, M.D., River Falls Medical Clinic, River Falls, Wisconsin. Phone 425-5322.

LAKE SHORE PROPERTY FOR RENT: For rent July, August, either/or, completely equipped 3-bedroom home on beautiful Lake Sylvan near Brainerd adjacent to the Pine Beach golf courses, 200 feet private sandy beach, screened patio, garden, walkout basement, fireplace. $800 a month. References required. Jerry Vessels, Route 6, Brainerd, phone 829-2065.

GENERAL PRACTITIONER WANTED to join well-established three man group in Twin City area. Starting salary $20,000.00 to $25,000.00 range with opportunity for early partnership; or, will negotiate. Write: Minnesota Medicine-424, 375 Jackson, St. Paul 55101.

TEN MAN MULTISPECIALTY group needs an ophthalmologist and another pediatrician. New clinic building, complete laboratory and x-ray facilities. 180 bed modern hospital across street from clinic. Early share-holders status. Salary open. Write or call the Lenont-Peterson Clinic, Ltd., C. A. Tietz, M.D., area code 218, 741-4292, Virginia, Minnesota 55792.

LONG LAKE NEEDS DOCTOR. Professional Bldg. for sale or rent. Has waiting room with reception counter, two toilets, lab-darkroom, large X-ray room plus five other rooms. Picker 100-100 Century available. Sublease area has large room and toilet, suitable for dentist or other Professional with shared waiting room. All new modern interior. Wide open; no Doctor in town. Jay R. Kallestad. A.C. 612-920-7687.

GENERAL PRACTICE—Excellent opportunity to join General Practitioner in western South Dakota community. Philip is located in the middle of rich ranching country. The community has modern 20 bed hospital with nursing home under construction. Modern clinic adjacent to the hospital. Tentative plans are to open day clinic in neighboring community of Wall, home of the famous "Wall Drug." Good hunting and fishing opportunities and within short drive of the beautiful Black Hills. For more information, write or call G. J. Mangulis, M.D., Philip, South Dakota or Mr. Ted Hustead, Wall, South Dakota.

Special Article

Value of Graphic Methods

in a Teaching Hospital

JOHN L. WANAMAKER, Lt. Colonel, USAF, MC*
Washington, D. C.

As a part of the program for teaching physical diagnosis to interns and residents during their tour on the Cardiology Service at Wilford Hall USAF Hospital, phonocardiograms and indirect pulse tracings have been recorded on a wide variety of patients. Since July 1965 approximately 1,200 graphic studies have been made on both ward and clinic patients. In this paper an attempt is made to evaluate the role of this method of study in the teaching program.

Recording Technique

The technique used at this hospital does not differ significantly from that of others[1] and will be described only briefly. The phonocardiogram is recorded in the four classical auscultatory areas with breathing suspended. Another recording is made during normal breathing with the pick-up in the pulmonic area in order to define the mobility of the two main components of the second heart sound. An indirect carotid pulse tracing is recorded simultaneously to permit study of its form and for timing of the phonocardiographic events. An apex cardiogram is recorded by placing the pulse pick-up over the point of maximum apex impulse; generally, it is obtained most readily by turning the subject from the supine to a more lateral position. The apex tracing is used to time the phonocardiographic events recorded at the mitral area. When indicated, other arterial pulse waves or the jugular venous pulse are recorded. An electrocardiogram lead is recorded simultaneously for an additional reference point for timing.

Using this technique, 90% of the tracings are recorded satisfactorily for interpretation. An illustrative study in which the phonocardiogram has been recorded in the mitral area is presented in Figure 1. The electrocardiogram can be recognized as the lower tracing; the apex cardiogram is directly above it. After

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atrial excitation, an outward movement of the apex is recorded. Attributed to presystolic left ventricular filling caused by atrial contraction, this movement is termed the A wave. The major outward movement of the apex is seen next; it begins slightly after ventricular excitation. This movement is believed to represent isometric left ventricular contraction, which ends with the onset of ventricular ejection—an event that corresponds to the E point on the ACG. During the remainder of left ventricular ejection and relaxation, the predominant motion of the cardiac apex is away from the chest wall. This withdrawal is arrested at 0, an event that times closely with mitral valve opening. Ventricular filling occurs in three phases: first, rapidly (RFW), then slowly (SFW), and finally, in the previously mentioned A wave resulting from atrial contraction.

The normal carotid pulse record shows a smooth rapid upstroke that rises to a single dominant peak: the percussion wave. The dicrotic notch, which is seen as a sharp indentation on the downslope, is very useful for identifying aortic closure and estimating the duration of left ventricular ejection.

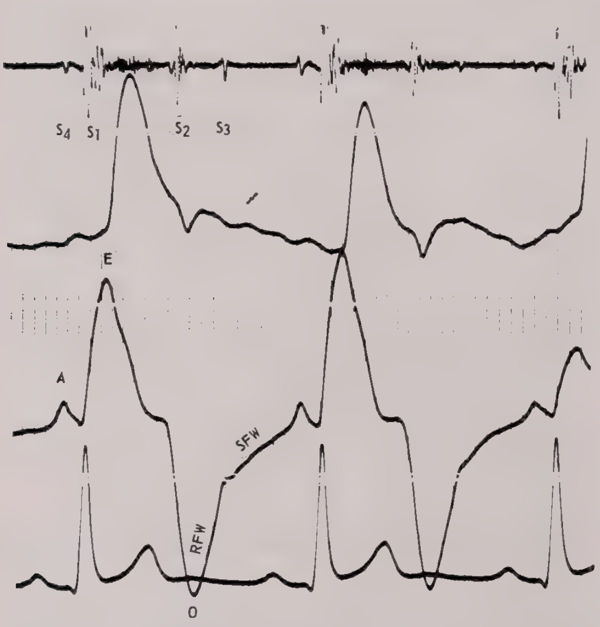

Fig. 1—A Typical Graphic Study. Lower tracing, lead II of electrocardiogram. Second tracing, apex cardiogram. A, E, O, RFW, and SFW refer to specific reference points as explained in text. Third tracing, carotid pulse. Top tracing, phonocardiogram: S_1, S_2, S_3, and S_4 refer to first heart sound, second heart sound, etc. A faint systolic murmur is present.

The phonocardiogram shows the four numbered heart sounds and their temporal relationships. The various portions of the study will be described in more detail later.

Benefits

With the possible exception of some low-frequency vibrations, it must be emphasized that the recording apparatus does not sense anything beyond the range of the physician's eyes, ears, and fingers; however, the tracings are objective and unbiased by historical, x-ray, or other data. One of the early benefits was to stimulate more careful physical examination and recording of findings, for the threat of being "scooped" by the recorder is ever present.

Separation of Cardiac Events

One major virtue of the graphic recordings is the ability to separate the various cardiac events into the proper time sequence. This ability is an inherent property of the recorder, but it can be developed in physicians only by experience and correlation with some reference point. The records provide a reliable point of reference.

Accurate timing of the events around the two heart sounds is essential for making judgments about disordered hemodynamics. Several of these events are shown in Figure 2. Splitting of the first heart sound is presumed to result from asynchronous closure of the mitral and tricuspid valves and is considered normal. Both of these sounds occur after the Q wave of the electrocardiogram and prior to the onset of the carotid upstroke. An ejection click focuses attention on one of the great arteries, or its semilunar valve. Both appear at a longer distance from the initial vibrations of the first sound and, if aortic in origin, they correspond to the onset of the carotid upstroke.

Hypertrophied Ventricle

A fourth heart sound, or atrial gallop, occurs during the P-R interval of the electrocardiogram. When this sound originates in the left ventricle, it is usually associated with a large A wave on the apex cardiogram. Physiologically the sound suggests a hypertrophied ventricle with elevated end-diastolic pressure[2]. . . . Occasionally a mid-systolic click can be confused with an ejection click. The phonocardiogram ends the confusion and indicates a change in the implication from one of great vessel disease to considerations of previous pericarditis or mitral regurgitation.[3,4]

Left Bundle Branch Block

Reversed splitting of the second heart sound may be difficult to identify at the bedside without considerable experience. The phonocardiogram with a carotid pulse for timing can make this phenomenon obvious. The reversed splitting of the second heart sound (Figure 3) was recorded from a patient with left bundle branch block. Although the reversed split is a common and reliable diagnostic feature of this conduction abnormality, it can be helpful for evaluating other problems. The presence

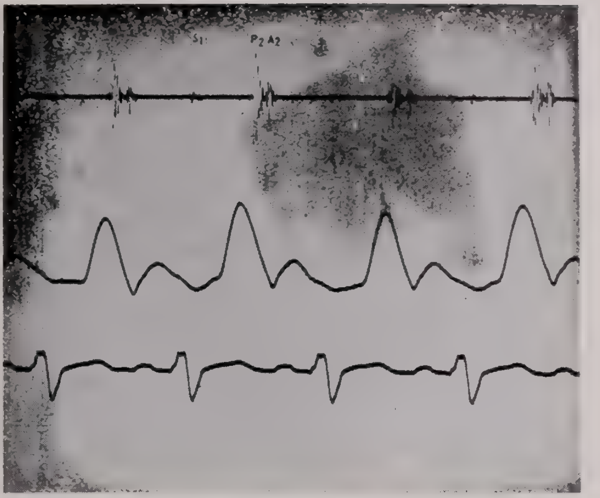

Fig. 3—Reversed Splitting of Second Heart Sound. Close temporal association of A2 with dicrotic notch on carotid pulse tracing identifies it as aortic closure. Occurrence of pulmonic closure prior to aortic closure establishes diagnosis of reversed splitting of second sound. Left bundle branch block is noted on accompanying electrocardiogram.

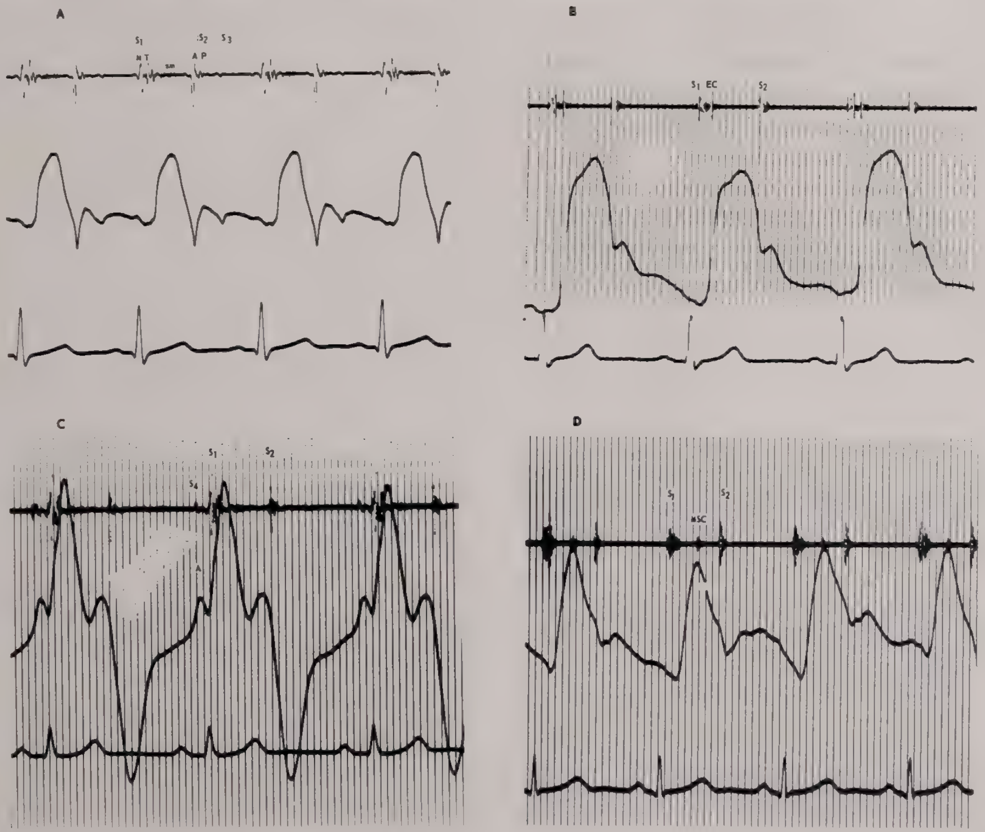

Fig. 2—Auscultatory Events Around First Heart Sound. (A) Split first sound. Separation between mitral (M) and tricuspid (T) is observed. Both occur after onset of QRS in electrocardiogram and before upstroke of the carotid pulse. (B) Aortic ejection click appears somewhat later and corresponds to upstroke of carotid pulse. (C) Fourth heart sound (S_4) on the phonocardiogram corresponds to A wave of apex cardiogram and occurs during the P-R interval of electrocardiogram. (D) Mid-systolic click (MSC) on phonocardiogram occurs well after onset of carotid pulse upstroke and well after QRS on electrocardiogram.

of this feature during an attack of chest pain can aid in establishing the diagnosis of ischemic heart disease.[5]

Specific Diagnoses

Some cardiovascular abnormalities have rather characteristic constellations of physical findings that lend themselves well to graphic analysis. In addition to aiding in clinical diagnosis, recordings of these abnormalities can serve as permanent displays in which the salient features can be emphasized for teaching purposes.

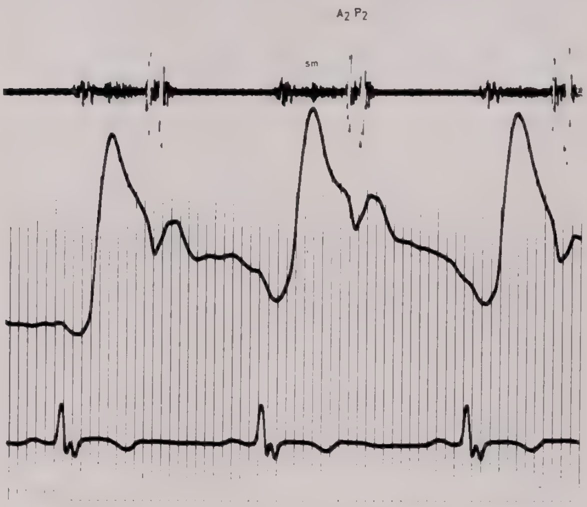

Fig. 4—Atrial Septal Defect. Phonocardiogram: systolic ejection murmur (SM), wide fixed splitting of S_2, accentuated pulmonic closure (P_2). Electrocardiogram: right ventricular conduction defect. Carotid pulse allows accurate timing of semilunar closure.

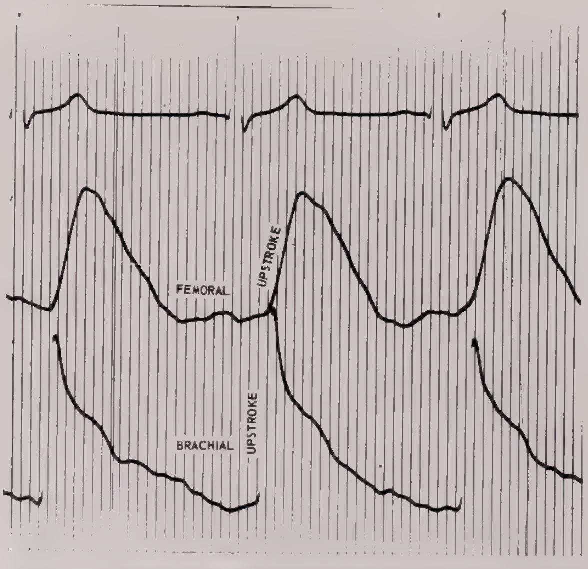

Fig. 5—Aortic Coarctation. Marked slowing of the upstroke is noted in the femoral pulse tracing. Brachial upstroke is normal.

Atrial Septal Defect

Figure 4 demonstrates the classic findings in the pulmonic area with an atrial septal defect, i.e., the systolic ejection murmur; the split second heart sound, which does not vary with respiration; and the prominent pulmonic closure. Many young men with systolic murmurs are evaluated annually in the Cardiac Clinic. The phonocardiogram has become a valuable screening tool for determining whether fixed splitting of the second heart sound is present in these patients.

Aortic Coarctation

Aortic coarctation is a curable form of hypertension that is frequently misdiagnosed. Simple palpation of the brachial and femoral pulses will allow one to make this diagnosis, for the difference in speed of the upstroke between the two pulses is quite striking. After seeing an example such as Figure 5, a physician is not apt to neglect examination of the femoral pulses in a hypertensive workup.

Patent Ductus

Another pathognomonic cardiovascular sign is the continuous murmur of patent ductus arteriosus, which may often be confused with the combined systolic and diastolic murmurs of aortic stenosis and aortic regurgitation. This is especially true if an adult presents with a previous diagnosis of aortic valvular disease and signs of a marked aortic run-off, like a recent patient at this hospital. Even after careful examination, several members of the staff were swayed into describing separate systolic and diastolic murmurs. The phonocardiogram (Figure 6) shows the continuous nature of the murmur with its peaking around the second heart sound and confirmed a central arteriovenous shunt.

Tricuspid Stenosis

At times, graphic methods may help to separate coincident lesions, as in the study of the young woman with rheumatic heart disease, as illustrated in Figure 7. Mitral stenosis was known to be present, but diagnosis of possible tricuspid involvement remained a problem. Inspiratory augmentation of the presystolic murmur at the tricuspid area, with simultaneous diminution in the one recorded at the mitral area, justified the diagnosis of tricuspid stenosis as a second lesion. The prominent A wave on the jugular venous pulse tracing was confirmatory. These diagnoses were documented at cardiac catheterization and surgical attack on both valves was successful.

As mentioned earlier, many Air Force recruits are screened in the Cardiology Clinic for systolic murmurs, many of which are presumed innocent in the absence of other cardiovascular abnormalities. Occasionally the

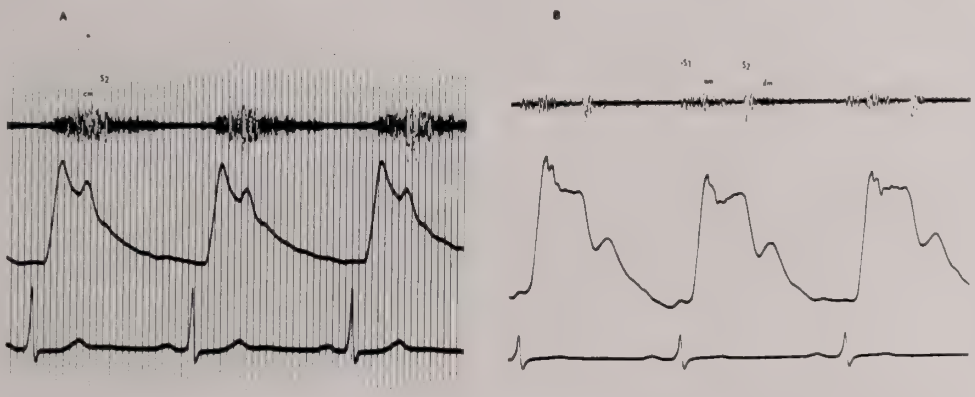

Fig. 6—(A) Patent Ductus Arteriosus. Phonocardiogram displays continuous murmur (cm) which peaks around second sound (S_2). It extends into mid-diastole. Carotid pulse tracing shows bisferiens nature characteristic of aortic run-off. (B) Combined aortic valve lesions. Systolic ejection murmur (sm) of aortic stenosis ends well before second sound (S_2). Semilunar diastolic murmur (dm) begins with S_2. Bisferiens carotid pulse noted.

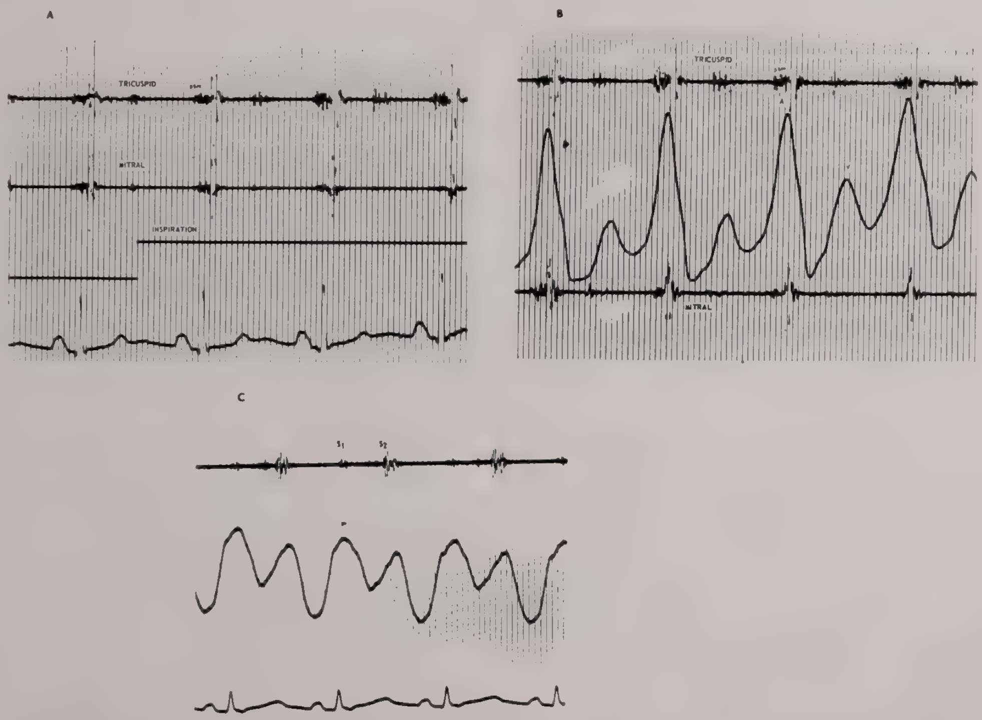

Fig. 7—Tricuspid and Mitral Stenosis. Inspiration increases amplitude of presystolic murmur (psm) in tricuspid phonocardiogram. The murmur of mitral stenosis is diminished with inspiration. (B) Very prominent A wave on jugular venous pulse from same case. (C) Postoperative tracing from same case. Diminution in height of A wave on jugular venous pulse. Reduction in presystolic murmur.

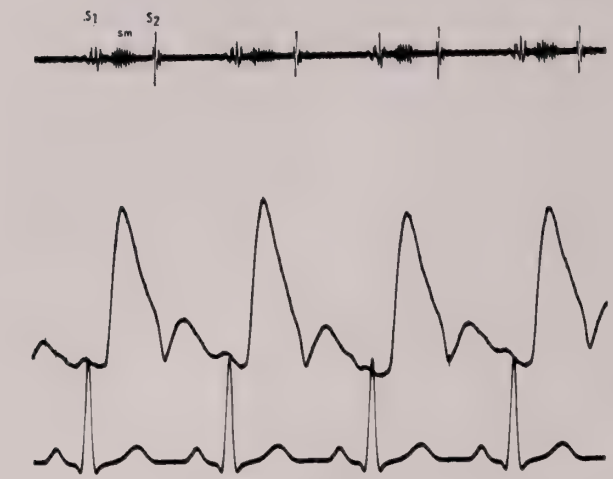

Fig. 8—Innocent Systolic Murmur. Systolic murmur (sm) with pure tone or vibratory quality.

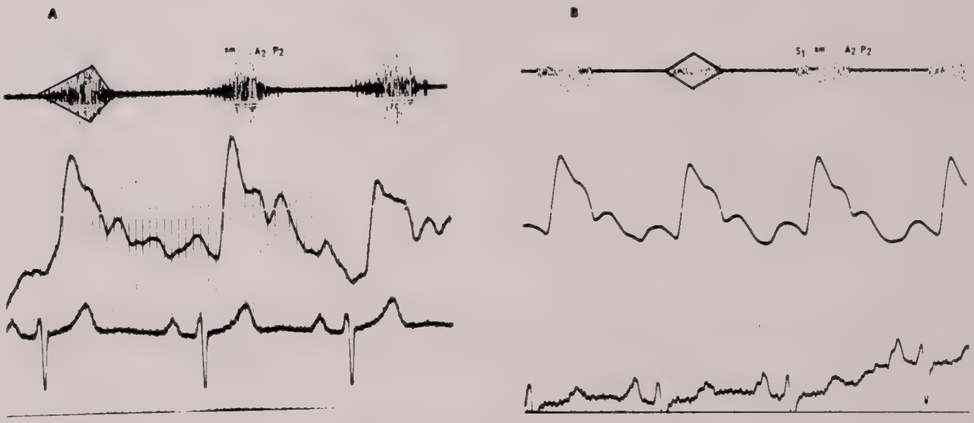

Fig. 9—Valvular Pulmonic Stenosis with Intact Ventricular Septum. Systolic murmur (sm) peaks late, partially obscures aortic closure (A_2), and persists beyond aortic closure. Wide split of second sound with delayed pulmonic closure (P_2). (B) Postoperative tracing from same case. Systolic murmur (sm) is shorter and peaks earlier than preoperative.

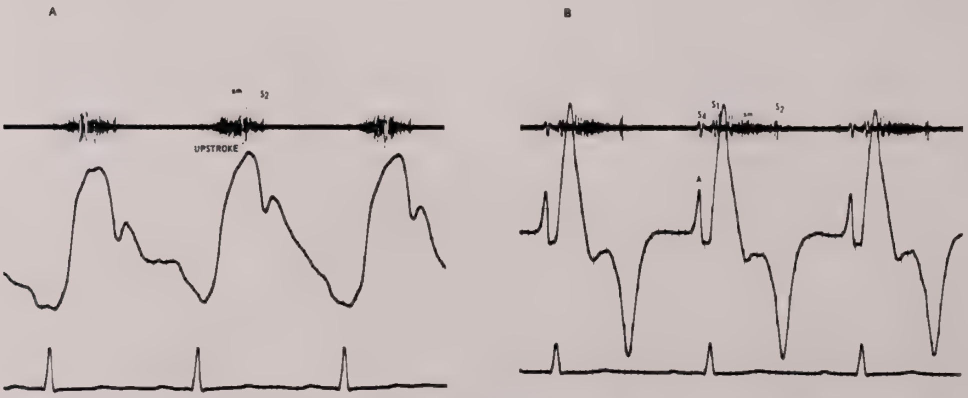

Fig. 10—Valvular Aortic Stenosis. (A) Phonocardiogram: systolic ejection murmur. Carotid pulse tracing: delayed and rounded upstroke. (B) Phonocardiogram: atrial gallop (S_4) corresponding to large A wave on apex cardiogram.

appearance of the murmur on the recording is characteristic of a pure tone or vibratory nature, and is useful in confirming its innocent origin.

Assessing Severity of Lesions

Pulmonic Stenosis

The severity of many cardiovascular lesions can be estimated quite accurately from the physical findings. Semi-quantitative evaluation of certain lesions may be made by analyzing graphic methods. A lesion of this type is pulmonic stenosis. Good correlation has been noted between the form and duration of the systolic murmur, the split second heart sound, and the peak systolic right ventricular pressure found at catheterization.[6] The recording of a patient with moderate pulmonic stenosis, a peak right ventricular pressure of 140 mm Hg and a gradient of 100 mm Hg across the pulmonic valve is shown in Figure 9. The murmur extends beyond aortic closure and peaks late, and the second sound is widely split in the preoperative recording. After successful surgery, the murmur is shorter and peaks earlier, and the split of the second sound is narrower.

Aortic Stenosis

Aortic stenosis differs slightly from pulmonic stenosis. Although the duration of the murmur may be of some help, it is often misleading when assessing the degree of obstruction. Narrow or reversed splitting of the second sound may be more helpful in evaluating prolongation of left ventricular ejection, or a fourth sound may indicate elevated left ventricular end-diastolic pressure. The most useful findings are those in the carotid pulse.[7] The slowed upstroke, systolic thrill, and prolonged ejection time can be appreciated at the bedside. On the indirect carotid pulse tracing they can be measured and the gradient estimated. Figure 10 illustrates the significant features in a patient with valvular aortic stenosis and a transaortic gradient of 80 mm Hg. Estimation of the severity of aortic stenosis is particularly important, because it may facilitate a decision regarding catheterization in this disease—a procedure that is attended with increased risk resulting from the need for some form of arterial puncture.

Mitral Stenosis

In some instances, cardiac catheterization may be impractical and even contraindicated. Graphic studies provide quantitative data under such circumstances. The example in Figure 11 is taken from a study of a 22-year-old woman in the first trimester of pregnancy who presented with symptoms of pulmonic congestion. The possible risk of irradiation to the fetus during catheterization was considered a relative contraindication to that procedure. The information presented in this illustration was sufficient for a diagnosis of mitral stenosis of surgical severity and led to successful commissurotomy.

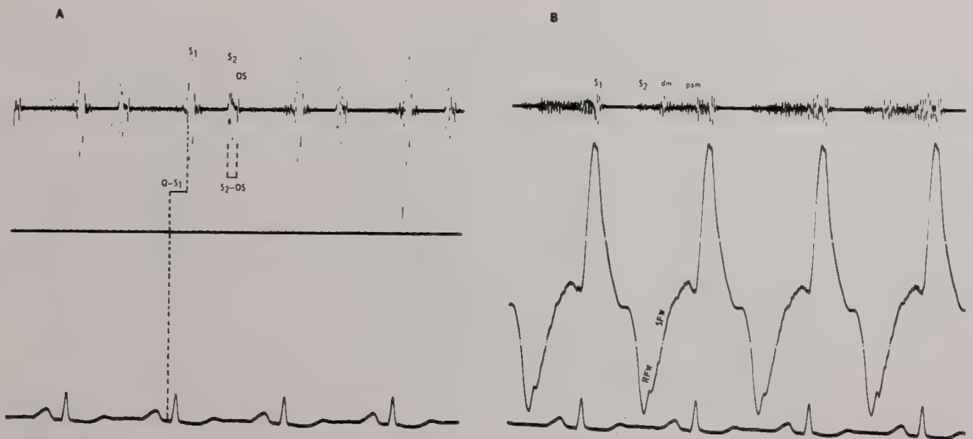

Fig. 11—Mitral Stenosis. (A) Method of determining Q-S_1 and II-OS intervals. Phonocardiogram is recorded in mitral area. (B) Phonocardiogram: diastolic murmur (dm) and presystolic murmur (psm). Apex cardiogram: blending of rapid filling wave (RFW) and slow filling wave (SFW) into single gradual diastolic wave.

Previous studies have established the prolongation of the Q-S_1 interval and the shortening of the II-OS interval in association with left atrial hypertension, secondary to the mitral obstruction.[8,9] When the Q-S_1 exceeds the II-OS interval, usually critical mitral stenosis is present. In this patient the II-OS interval is 0.05 seconds, and the Q-S_1 interval 0.09 seconds.

Another measure of mitral block is the alteration in the left ventricular filling pattern observed with this condition.[10] The apex cardiogram includes a gradual filling wave that does not show the usual neat separation between the rapid and the slow-filling phases. It is well illustrated in Figure 11, which also shows the typical opening snap and the diastolic murmur of mitral stenosis.

Evaluation of Therapy

Graphic studies can be used to evaluate the effects of treatment as well as to estimate the severity of certain lesions and follow their progression. The reappearance of a rapid filling wave on the apex cardiogram is a convenient method of assessing the hemodynamic benefit of mitral commissurotomy. Preoperative and postoperative tracings of a 35-year-old woman are shown in Figure 12. The transition from the gradual filling slope to one with distinct rapid and slow filling phases is apparent and indicates effective relief of the mitral obstruction.

Another example of serial tracings (Figure 13) pertains to a patient who had mitral valve surgery. The preoperative tracing made with

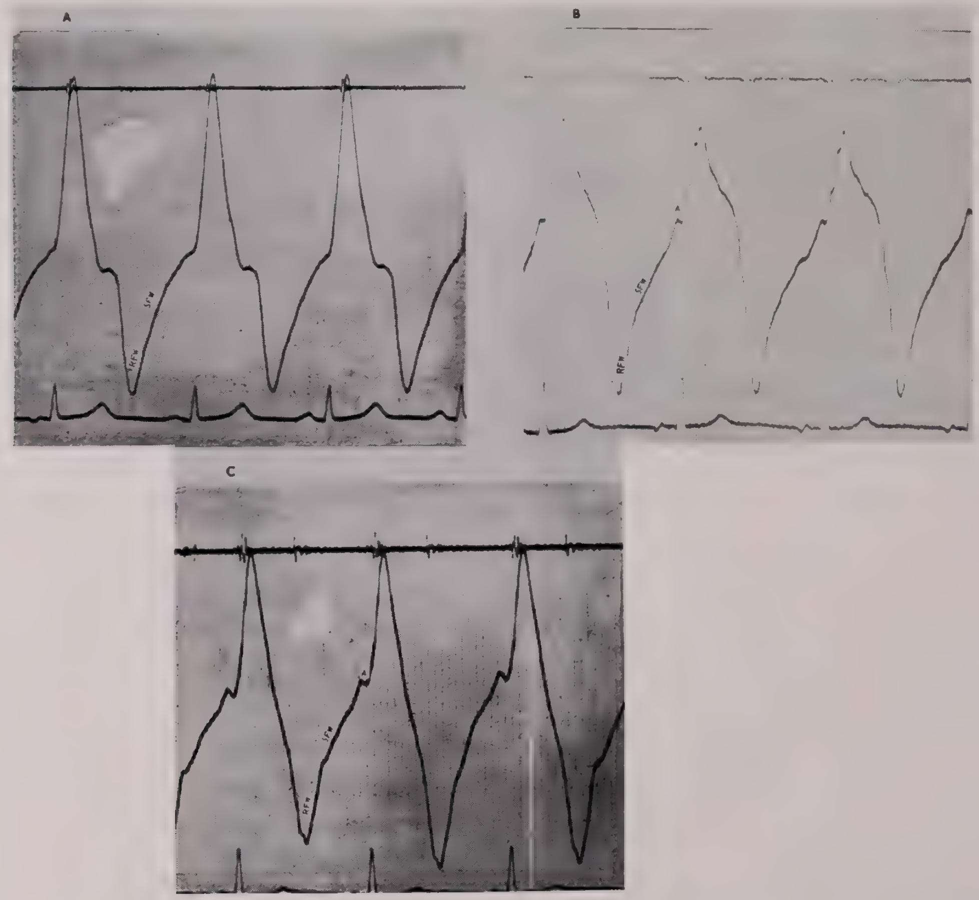

Fig. 12—Mitral Stenosis. (A) Preoperative tracing. Apex cardiogram: no recognizable separation between rapid filling wave (RFW) and slow filling wave (SFW). (B) Phonocardiogram and apex cardiogram three weeks postoperatively. Distinction between RFW and SFW now apparent. Return of A wave. All are evidence of relief of obstruction. (C) Tracing six weeks postoperatively; better definition of RFW, SFW, and A waves.

the phonocardiogram recorded in the mitral area shows the typical systolic regurgitant murmur, the mitral opening snap, and the ventricular gallop corresponding to the top of an accentuated rapid filling wave on the apex cardiogram that comprise the diagnostic findings of mitral regurgitation. The ventricular gallop is followed by a short flow rumble, which attests to the hemodynamic significance of the mitral leak. The postoperative study shows the sharp clicks associated with the closing and the opening of the mitral prosthesis. The systolic murmur is markedly diminished; the ventricular gallop and diastolic flow murmur are no longer present; and the diastolic motion of the apex is more nearly normal.

Some Surprises

Although we have emphasized that all of the information on the graphic recordings is available at the bedside, sometimes it is neglected or misinterpreted by the physician. On these occasions the tracings can teach the important lesson of humility and serve as a valuable supplemental method of study. Two examples are presented to illustrate this. The first tracing (Figure 14a) was made to evaluate chest pain and an atypical systolic murmur

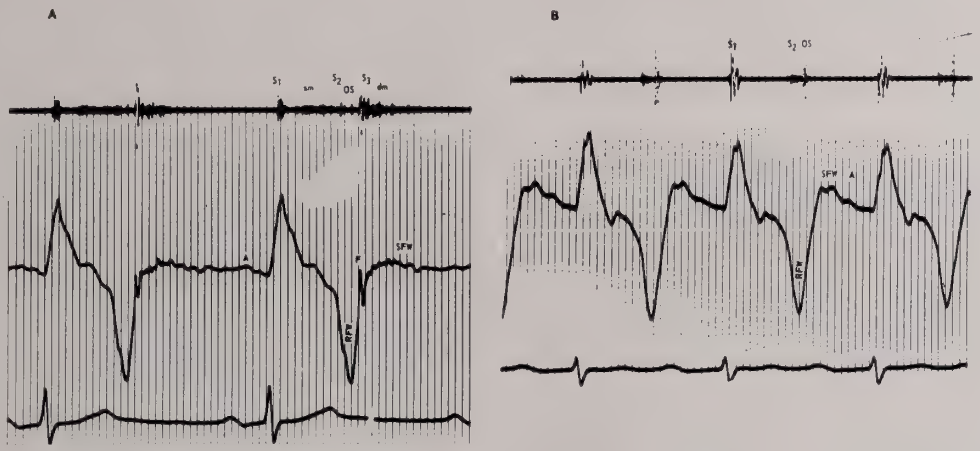

Fig. 13—Mitral Regurgitation. Preoperative tracing. Phonocardiogram: systolic murmur (sm), opening snap (os), ventricular gallop (S_3), and diastolic flow murmur (dm). Apex cardiogram: accentuated rapid filling wave (RFW) with significant peak (F), corresponding to ventricular gallop. (B) Postoperative replacement with Starr-Edwards prosthesis. Phonocardiogram: augmented opening sound of prosthetic valve (OS). Absence of previous murmurs. Apex cardiogram: disappearance of (F) wave and more normal behavior of RFW and SFW.

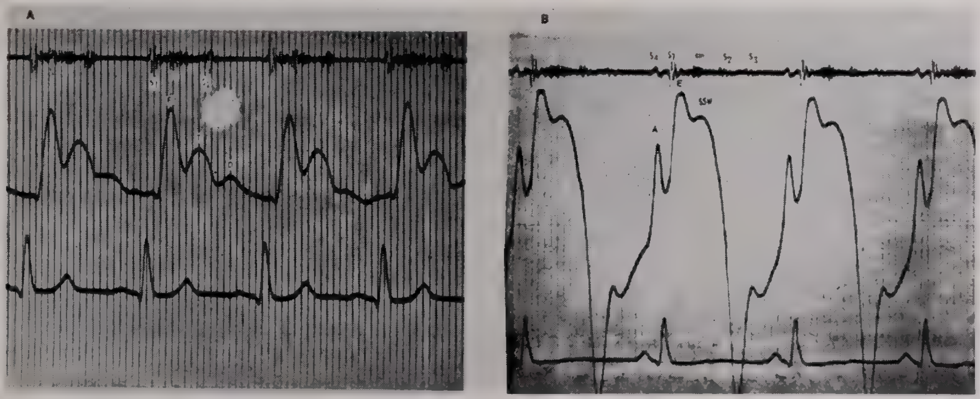

Fig. 14—Muscular Subaortic Stenosis. Phonocardiogram: systolic ejection murmur (sm). Reversed split of second sound (S_2). Carotid pulse tracing: prominent tidal wave (T) in combination with percussion wave (P) and dicrotic waves (D) produce typical m shape of carotid pulse. (B) Phonocardiogram at apex: atrial gallop (S_4) and ventricular gallop (S_3) corresponding respectively to augmented A wave and top of rapid filling wave on apex cardiogram. Apex tracing also shows second systolic bulge (SSW), another characteristic of this lesion.

in a young man. During a cardiology teaching conference, at which his case was presented, the physical examination was conducted by an experienced cardiologist, but no definitive diagnosis was made. Perusal of the carotid tracing later disclosed the typical m-shape curve[11] that is characteristic of muscular subaortic stenosis. This diagnosis was confirmed at cardiac catheterization. The atrial and ventricular gallops, which can be part of this syndrome as well as the characteristic second systolic wave on the apex tracing, are seen in Figure 14b.

Figure 15 illustrates the use of graphic studies for indicating the presence of unusual physiology, which is not always appreciated clinically. The patient was a 26-year-old woman who had undergone successful mitral replacement with a Starr-Edwards prosthesis in 1966. On a routine follow-up two years later, she was believed to be suffering from mild digitalis toxicity. An indication of this condition is the markedly prolonged P-R interval on the electrocardiogram. However, the unusual sound pattern of the prosthetic valve was not appreciated clinically. The first sound, which is very faint, lacks the prominent high frequency component that is characteristic of prosthetic valve closure. On the other hand, a prominent opening click occurs at the appropriate time in diastole. A similar click that occurs somewhat later in diastole suggests a prosthetic origin.

Examination of the electrocardiogram and the apex cardiogram indicates that atrial contraction must occur at about the time that the prosthesis opens. Early ventricular filling is then accomplished both passively and by active atrial contraction. It was thought that the combined mechanism of ventricular filling was effective in raising left ventricular pressure above left atrial pressure prior to the onset of left ventricular systole and led to premature closure of the prosthetic valve. Unfortunately, this speculation remained untested, for digitalis had been stopped and the patient had returned to her home before this fascinating graphic study was analyzed. This study illustrates again how use of the Graphic Laboratory can reveal previously overlooked, but significant physical findings and how careful analysis of the tracing can contribute to an understanding of the disordered hemodynamics.

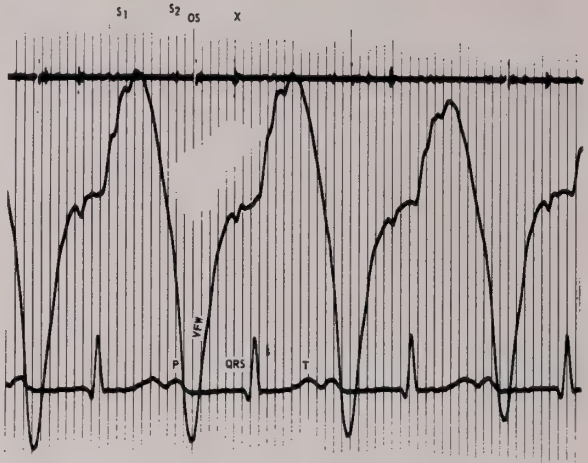

Fig. 15—Starr-Edwards Prosthesis with First Degree Heart Block. Phonocardiogram: first sound (S_1) is reduced in amplitude. The opening sound (OS) of the prosthetic valve corresponds to the 0 point on the apex cardiogram. High frequency sound (X) occurs in mid diastole at the top of ventricular filling wave, (VFW), of accompanying apex cardiogram. Electrocardiogram documents prolonged atrioventricular conduction with P-R interval 0.36 sec.

Summary

A review of about 1,200 graphic studies of the cardiovascular system has indicated their value in teaching physical diagnosis. The tracings serve as a reference that the physician can consult in checking his findings. Some types of cardiovascular lesions have graphic representations that are sufficiently characteristic for making the diagnosis as well as giving instruction on the typical findings. An analysis by graphic methods also permits semi-quantitation of the lesions, and this information is valuable in deciding whether to do a cardiac catheterization or surgery if a catheterization is not feasible. The physician also can follow the progress of some lesions and assess the effectiveness of the surgical treatment. On occasion, these studies have indicated diagnoses not previously apparent. Graphic methods are not only safe and easy to use, but also of considerable value to the teaching program at Wilford Hall USAF Hospital.

Acknowledgment

To the following people: TSgt Dale Gindlesperger and Mrs. Beatrice Hays, whose diligence and technical skill produced the recordings; Mrs. Lydie Dyer, whose facility with language transformed the manuscript into English; and Mrs. Mary L. Richardson, who coordinated the effort and carried it through to completion, most sincere appreciation and gratitude are extended.

References may be secured from the author or the reprints.

Book Reviews

Books are the compasses and telescopes and sextants and charts which other men have prepared to help us navigate the dangerous seas of human life.—Jesse Lee Bennett

RECENT ADVANCES IN MEDICINE—Edited by Baron, Compston and Dawson. 433 pages. Published by Little, Brown & Co., 34 Beacon Street, Boston, Mass., 15th Edition, June 1968. Price $15.50.

This is the 15th edition of a well established review book, first published in 1924. The editors state in their foreword, "The chapters are intended to be readable and critical surveys of important subjects and are written by authors actively working in those fields. Once again they are designed for undergraduate and postgraduate students, as well as for consultants and general medical and scientific readers, rather than for specialists in their respective fields."

This volume succeeds beautifully in the stated aims and covers the following topics: Computers in Medicine, Diseases of Muscle, Coagulation Disorders, Poisoning, Disorders of the Adrenal Cortex and Pituitary Gland, Iron Metabolism, Clinical Pharmacogenetics, Systemic Mycoses, Hypertension, Leukemia, Temperature Regulation and Its Disorders, Environmental Factors in Disease, and Cardiac Infarction and Cardiac Resuscitation. Sixteen distinguished contributors have produced brief, concise readable reviews which are noteworthy for their crisp styling and clever phrasing. While all the chapters are well done, the essays on Computers in Medicine, Poisoning, Clinical Pharmacogenetics, Temperature Regulation and Environmental Factors in Disease are worthy of special comment.

One cannot help but compare this review with its American counterparts, namely, the Annual Reviews of Medicine and the Advances in Internal Medicine. It is regrettable that certain subjects, such as the treatment of newer diuretics, transplantation immunology, polypeptide hormone assays and recent advances in pharmacology, such as the development of propanolol and newer antibiotics, have been omitted from the British volume.

This book makes up for any deficiencies in editorial selection of titles by its beautiful prose style, clarity and brevity. The volume is handsomely bound and deserves a place on the bookshelves of practitioners and consultant physicians alike.

Steven C. Beering, Lt. Colonel, USAF, MC, F.A.C.P.
Chief, Internal Medicine Service

COOPERATIVE STUDY ON CARDIAC CATHETERIZATION. By E. Braunwald, M.D., Professor and Chairman, Department of Medicine, University of California, San Diego School of Medicine, La Jolla, California; H. J. C. Swan, M.B., Ph.D. Director, Department of Cardiology, Cedars Sinai Medical Center, Los Angeles, California; American Heart Association, Inc., New York, 1968; 113 pp., $2.25.

Between the covers of this imposingly titled book is data on the mortality and morbidity of cardiac catheterization based on analysis of 12,367 procedures performed in 16 laboratories between 1 November 1963 and 31 October 1965. Today, with catheterization a widely used diagnostic tool and with many physicians performing similar procedures, e.g., central venous pressure monitoring, this type of information is of inestimable value.

The book is a compilation of statistical data with case reports to illustrate specific points. Each chapter is complete in itself and has been written by one or more of the six collaborating physicians. Chapters deal with design and data handling incident to the study; with specific complications, e.g., arrhythmias; with specific groups, e.g., infants; and with specific procedures, e.g., coronary arteriography.

Although not included in the purpose of the study, I would have liked some concrete suggestions to minimize the complications reported. A chapter, "Alterations in Catheterization Techniques During the Course of the Study," only hinted at this. The group of outstanding cardiologists who conducted this study are uniquely qualified to draw such conclusions on the basis of their data.

All in all, this book contains a wealth of statistical data and is well worth the $2.25 out of any physician's pocket.

Eliot Schechter, Lt. Colonel, USAF, MC
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Meetings and Announcements

This world, where much is to be done and little to be known.—Samuel Johnson

MARCH

Hennepin County Medical Society
Regular Meeting, Pick-Nicollet Hotel, Minneapolis, 6 P.M., March 3.
Scott-Carver County Medical Society
Regular Meeting, Wagner's Supper Club, Jordan, 6:30 P.M., March 4.
Zumbro Valley Medical Society
Regular Meeting, Mann Hall, 7 P.M., March 5.
Minnesota Academy of Medicine
Town & Country Club, St. Paul, 6 P.M., March 12.
Minnesota Academy of Ophthalmology & Otolaryngology
Regular Meeting, Minnesota Club, St. Paul, Dinner, 7 P.M., Meeting 8 P.M., March 14.
Steele County Medical Society
Inn Towne Motel, Owatonna, 6:30 P.M., March 18.
Blue Earth Valley Medical Society
Regular Meeting, Interlaken Golf Club, Fairmont, 7 P.M., March 19.
McLeod County Medical Society
Regular Meeting, 6:30 P.M., March 20, Location to be announced.
Stearns-Benton County Medical Society
Regular Meeting, Wagon, Wheel, Waite Park, 6:30 P.M., March 20.
Twin City Urological Society, Town & Country Club, 6:00 P.M., March 21.
Blue Earth County Medical Society meeting, Century Club, 7 P.M. March 24.
Range Medical Society
Executive & General Meeting, Hibbing, Dinner, 7:15 P.M., March 25.
Waseca County Medical Society
Regular Meeting, Waseca Memorial Hospital, 6:30 P.M., March 31.

APRIL

Scott-Carver County Medical Society
Regular Meeting, Wagner's Supper Club, Jordan, 6:30 P.M., April 1.
Brown County Medical Society
Spring Meeting, Orchid Inn, Sleepy Eye, 7 P.M., April 8.
Winona County Medical Society
Regular Quarterly Meeting, Williams Hotel, 7 P.M., April 8.
Minnesota Academy of General Practice
House of Delegates—Hotel Radisson, 1:30 P.M., April 8.
Spring Refresher—Hotel Radisson, 9:00 A.M.-5:00 P.M., April 9-10.
Minnesota Academy of Medicine, Town & Country Club, 6:00 P.M., April 9, St. Paul.
Minnesota Academy of Ophthalmology & Otolaryngology
Regular Meeting, Minneapolis Athletic Club, Dinner, 7 P.M., Meeting, 8 P.M., April 11.
Blue Earth Valley Medical Society
Regular Meeting, Interlaken Golf Club, Fairmont, 7 P.M., April 16.
McLeod County Medical Society
Regular Meeting, 6:30 P.M., April 17, Location to be announced.
Freeborn County Medical Society
Dinner Meeting, 7 P.M., April 17, Location to be announced.
Stearns-Benton County Medical Society
Regular Meeting, David's (South of St. Cloud on Highway No. 152), 6:30 P.M., April 17.
Twin City Urological Society
Town & Country Club, 6 P.M., April 18.
Waseca County Medical Society
Regular Meeting, Waseca Memorial Hospital, 6:30 P.M., April 28.
Blue Earth County Medical Society Meeting,
Century Club, 7 P.M., April 28.

Electroencephalography Course

A Course in Current Problems in Electroencephalography: Advances toward their Solution; Date: March 13-15, 1969, Place: Houston, Texas. Sponsors: The American Electroencephalographic Society and Baylor University College of Medicine. For further information contact: Dr. Peter Kellaway, Baylor University College of Medicine, Texas Medical Center, Houston, Texas 77025.

Minnesota Heart Association Seeks Young Scientists

Applications are now available for two months of study at either the Mayo Graduate School of Medicine or the University of Minnesota, through the MHA high school summer fellowship program.

Twenty students will be chosen and assigned projects with heart researchers. In addition, they will be awarded a $400.00 stipend. Students selected from outside the Twin Cities or Rochester areas will be given an additional $200.00 for room and board.

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Deadline for applications is April 1, 1969, and notification of the scholarship awards will be made by April 30, 1969.

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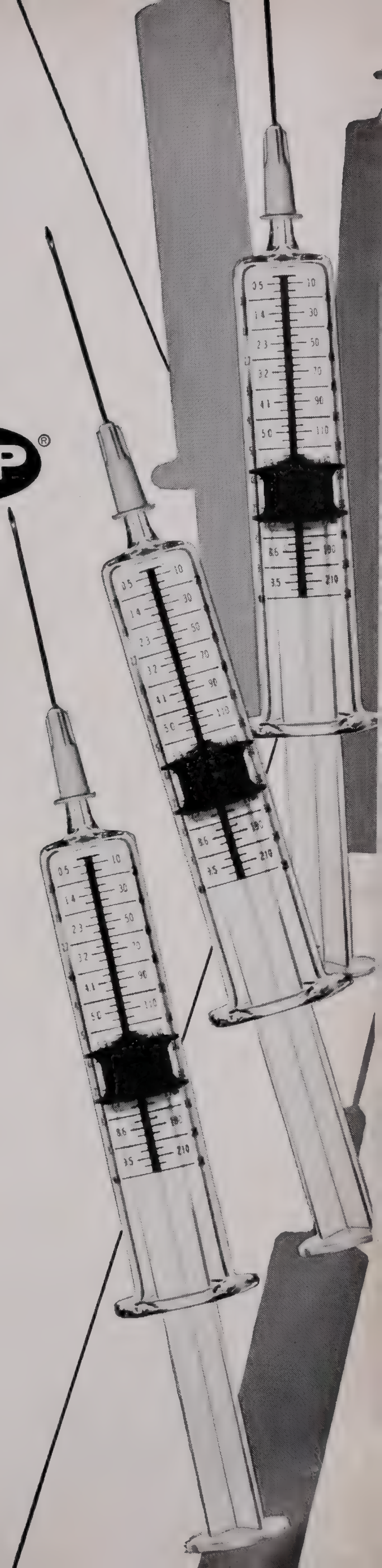

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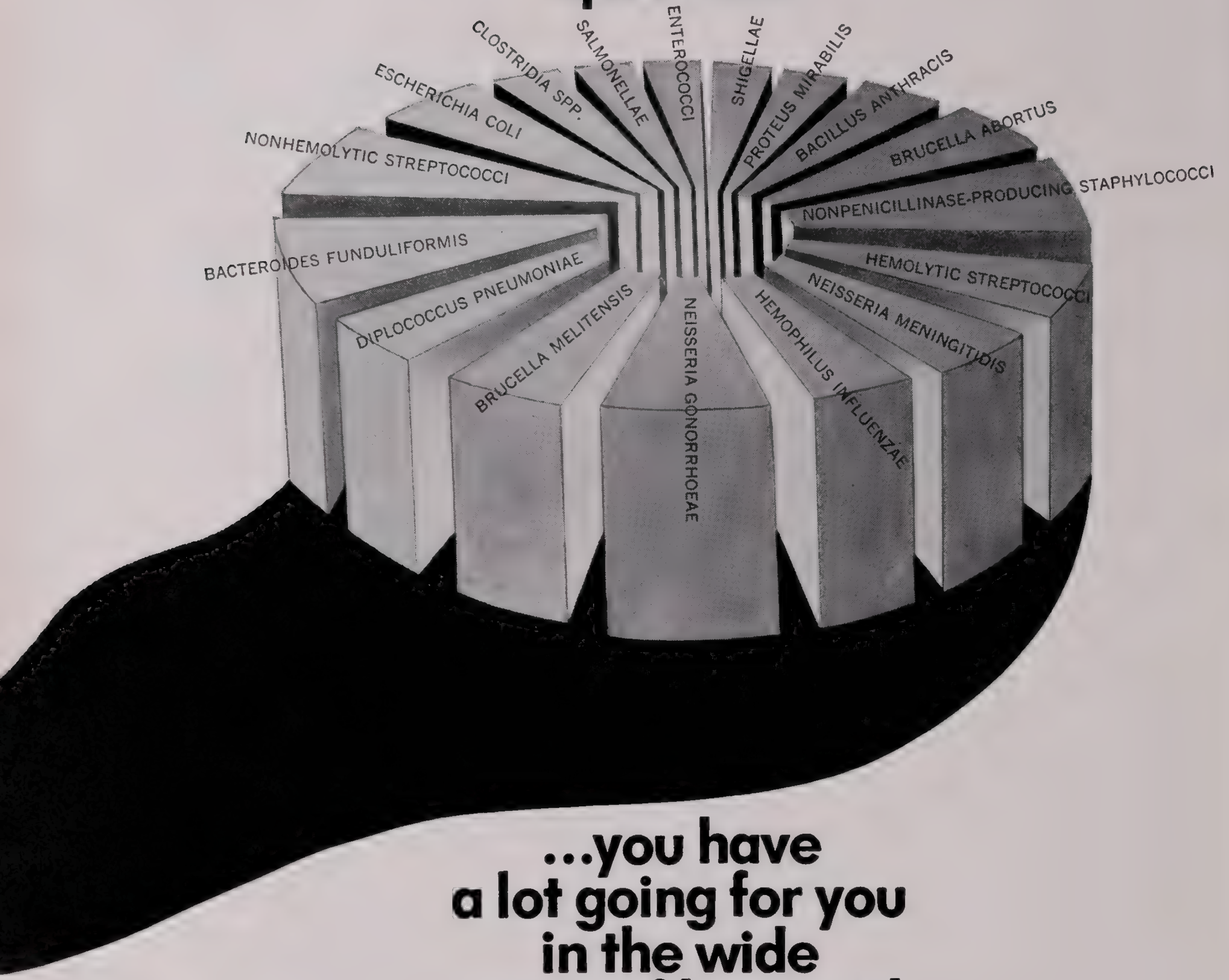
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Chairman's Letter

Eighteen Years of the Physicians' Assistance Committee

THE PHYSICIANS' ASSISTANCE COMMITTEE of the Minnesota State Medical Association has the duty of caring for elderly physicians in Minnesota who have come upon evil days. Most members of the Association are completely unaware of the fine work being done by this industrious committee in their behalf. It is felt that the labor of this devoted group is worthy of note on completion of eighteen years of quite effective effort.

It has long been recognized that physicians were especially prone to be lax in retirement planning. Of all the learned professions the physician generally prospered best and planned the least. He planned to practice forever, and even today physicians find it hard to believe that they may some day not be fit mentally or physically to continue seeing patients. The number of truly needy elderly physicians was never great and generally of local interest only.

Nationwide, twenty-five medical societies, either state or county, have permanent assistance committees with planned income almost always from dues. The Philadelphia Medical Society Assistance Committee was formed in 1778 and is the largest and most successful. They operate on a budget of about $36,000 a year, half from funds contributed yearly and half from interest on invested capital of several hundred thousand dollars.

The late Dr. Wade Humphrey of Stillwater saw the chaos in the multiplicity of plans and thought at first that a committee could function with voluntary donations. He went to the Council in 1951 and was given a committee who sent an appeal to all members of the Association. The results were sickening! This sad response served the purpose of igniting Dr. Humphrey, and he appeared before the House of Delegates hopping mad in the memorable and acrimonious session in Duluth in 1953. His eloquence prevailed and the delegates voted a special $10.00 per member assessment to put the Physicians' Assistance Committee in business; $26,708.00 was collected and the Physicians' Assistance program was off and running.

The basic policy has been that no physician or his widow should draw direct relief or O.A.A. monies. The Committee in 1956 requested a yearly dues raise of $4.00 per member with the money ear-marked for Physicians' Assistance. Many of those in need have some small income and need supplementary help. The largest grant to an individual has been $160.00 monthly, and some have received as little as $25.00. Cases come to the attention of the committee by communication to a county medical society from a member. Mr. Harold

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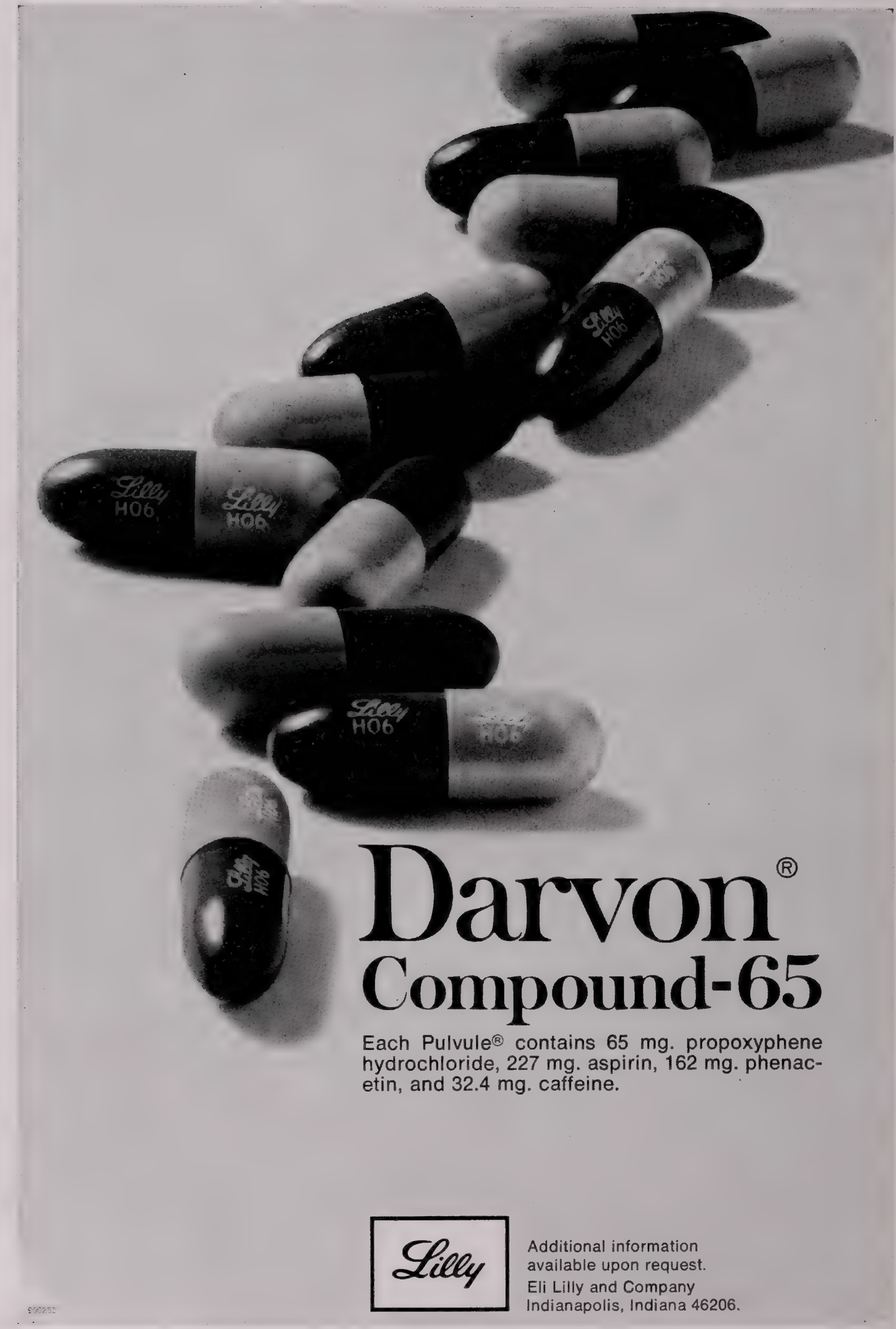

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Hodgkin's Disease

Current Views on Management

Y. MARUYAMA, M.D.*
Minneapolis, Minnesota

HODGKIN'S DISEASE is a disease involving lymph nodes and lymphoid tissue. Because it forms tumor masses, can be progressive and can lead to a fatal outcome, it is considered a malignant condition. However, the histological picture is extremely complex with a heterogeneity of cell types including lymphocytes, fibrosis, eosinophils, and large multinucleate giant cells. These last, known as Reed-Sternberg cells, are the *sine qua non* for the histopathological diagnosis. However, the disease may not be truly neoplastic, as commonly understood; indeed, profound lymphocytopenia and immunological deficiencies are regularly associated with it.

Treatment of Hodgkin's is presently based upon clinical staging, and this method of classification has been shown to correlate with prognosis. Classification based on histopathological features of biopsy specimens has generally been less satisfactory. However, the recently proposed criteria of Lukes and Butler[1] appear to offer useful histological criteria and another parameter to assess prognosis. They are: (1) lymphocytic predominance, (2) nodular sclerosis, (3) lymphocytic depletion, and (4) mixed cellularity. Keller et al.[2] recently reported a five-year actuarial survival of 90-100% for disease with histologic features of lymphocyte predominance. Similarly nodular sclerosis, although less favorable than the above, showed twice the survival rate of lymphocyte depletion or mixed cellularity at five years. For anatomic stage I and II disease both lymphocyte predominance and nodular sclerosis carry excellent five-year prognoses. Because of rapidly changing views regarding the disease, it is timely to review current theories regarding staging, therapy, and prognosis.

Clinical Staging

Management and treatment of Hodgkin's

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*Associate Professor of Radiotherapy, Division of Radiotherapy, Department of Radiology, University of Minnesota Hospitals.

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disease depend on the number of sites of glandular involvement by the disease process. Proper clinical management is dependent on accurate staging of the state of the disease. The treatment and prognosis are based upon staging of the clinical extent of disease, as recently modified[3] from the original staging system proposed by Peters and Middlemiss.[4]

Stage I

Disease limited to the lymph nodes of one anatomic region (I_1) or two contiguous anatomic regions (I_2) on the same side of the diaphragm.

Stage II

Nodal disease of more than two contiguous anatomic regions or in two noncontiguous regions on the same side of the diaphragm.

Stage III

Disease on both sides of the diaphragm but not extending beyond the involvement of lymph nodes, spleen or Waldeyer's ring* (limited to lymphatic tissues).

Stage IV

Disease involvement, in addition to lymph nodes, spleen or Waldeyer's ring of the bone marrow, lung parenchyma, pleura, liver, kidneys, gastrointestinal tract or any tissue or organ (extralymphatic sites).

These are further divided into A or B by the presence or absence of systemic symptoms such as fever, night sweats, pruritis, or weight loss in excess of 10 percent of normal weight. The designation of "B" is for the presence of systemic symptoms and is one of the most unfavorable of the prognostic indicators. It should be noted that disease of non-lymphoid organs cannot be staged by this scheme; in fact, a single extranodal site may be involved without lymph node disease and still carry an excellent prognosis (e.g., gastrointestinal tract[5] or lung).

Clinical Evaluation

The importance of accurate clinical staging requires that clinical evaluation be complete and accurate. Accurate staging requires careful history taking with particular attention to the systemic symptoms noted above. Physical examination should include palpation of all lymph node sites, visualization of the tonsillar fossa and nasopharynx, and examination for the presence or absence of an enlarged liver and spleen. Radiographic studies should include a chest and bone survey, intravenous

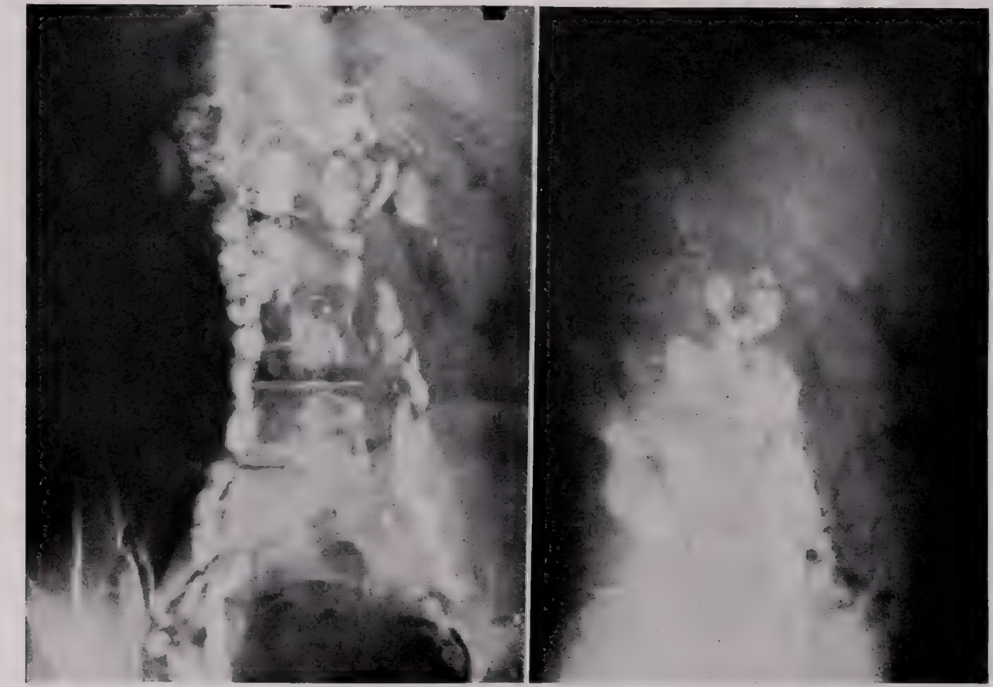

Fig. 1—Lymphangiogram showing extensive lymphomatous involvement of retroperitoneal nodes. The patient was asymptomatic and presented with a single enlarged gland in the cervical region.

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*See Test Your Word Score Page 672.

pyelography, and bilateral foot lymphangioadenography (LAG) to evaluate the retroperitoneal lymph nodes. The latter study has been found to be associated with little hazard when properly done,[6] and provides valuable information regarding the position and extent of involvement of these poorly accessible structures.

At one time clinical evaluation was based on physical findings, chest x-ray and clinical chemistry; at the present time, it cannot be considered complete without complete radiographic evaluation. Lee[7] found that lymphadenopathy in the groin (in the absence of other adenopathy) was nearly always associated with radiographically abnormal retroperitoneal nodes (Figure 1). Similarly, most patients with systemic symptoms ('B') may have abnormal retroperitoneal nodes. Thus, accurate clinical staging requires lymphangiographic study and evaluation of retroperitoneal lymph nodes.

From the history, physical examination, x-ray and clinical chemistry studies, preliminary staging can be made. Biopsy of accessible nodes will provide the histopathological diagnosis. Additional studies of great value are tomography of the lung and mediastinum, and needle biopsy of the liver, bone marrow or other organs, if under suspicion of involvement.

Accurate clinical evaluation and staging will permit appropriate therapeutic management.

Therapeutics of Hodgkin's Disease

David Karnofsky, the eminent chemotherapist, has succinctly stated the case for the choice between radiotherapy and chemotherapy: *"Radiotherapy has the first priority in planning an appropriate therapeutic program."* Nevertheless, chemotherapy has acquired an important role in the management of advanced, disseminated, and symptomatic Hodgkin's disease, and has greatly improved the general status of the patient with active Hodgkin's disease.

However, the view that radiotherapy has first priority must not ignore the fact that the quality of the therapy must also be top rate to obtain optimal results. Many radiologists would treat these tumors with small doses and small irradiation fields, following the earlier view that the disease is widespread and multi-focal at the time of clinical diagnosis, and that radiation can therefore only palliate an ultimately fatal disease. Moreover, the rapid shrinkage and response to radiotherapy had led to the view that the tumor was "radiosensitive" and therefore required only small radiation doses. (An example of response of a mediastinal mass to radiotherapy is shown in Figure 2). *This view is now regarded as incorrect.*

Stenstrom of the University of Minnesota early adopted the view that extended field therapy and large treatment doses might cure some of the patients afflicted with this condition. Hence the University of Minnesota in

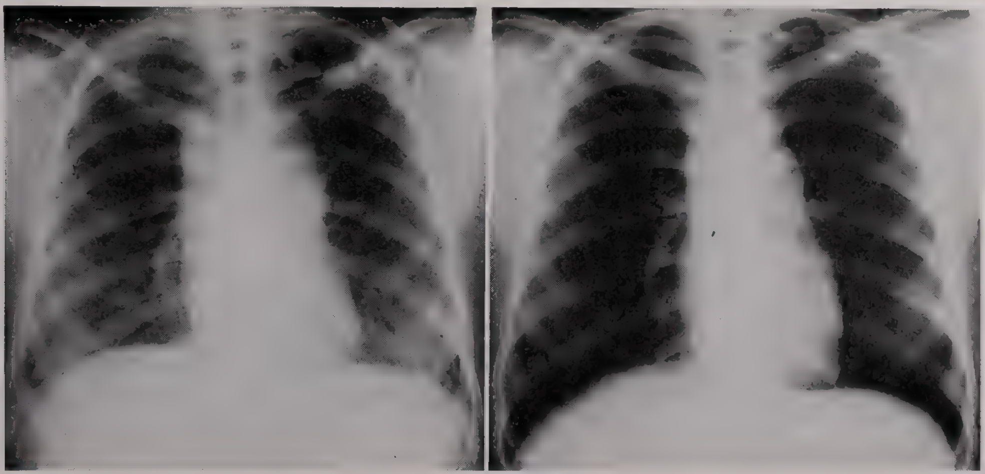

Fig. 2—Mediastinal mass and left supraclavicular lymphadenopathy shown by contrast medium following lymphangioadenography study (left). Following radiotherapy, mass and nodes show marked shrinkage with moderate (3500 rad) radiation dose.

1954[8] was able to report a series of patients treated with the intent to cure. In Stage I and II disease that aim was achieved in 90 percent for a five-year period (for Stage I, 17/20 and Stage II, 18/20). In Stage I, 77 percent (10/13) were surviving 10 years after treatment. This represents one of the outstanding therapeutic experiences reported for this disease. Extremely important to these results is the relationship to clinical staging as shown in Figure 3. For Stage III disease 10 percent (17/168) survived five years and 2 percent (3/143) for 10 years.

For Stage I and II (localized) disease the aim of therapy is cure. The best means to achieve this aim is with radiotherapy. Such treatments are best given with megavoltage equipment to large fields, shielding with lead blocks normal structures such as lung and spinal cord (Figures 4 and 5). Treating a single large field is generally more satisfactory than the practice of treating multiple small fields, the junctions of which may under- or overlap, leading to uncertain tumor doses in the junctional zone.

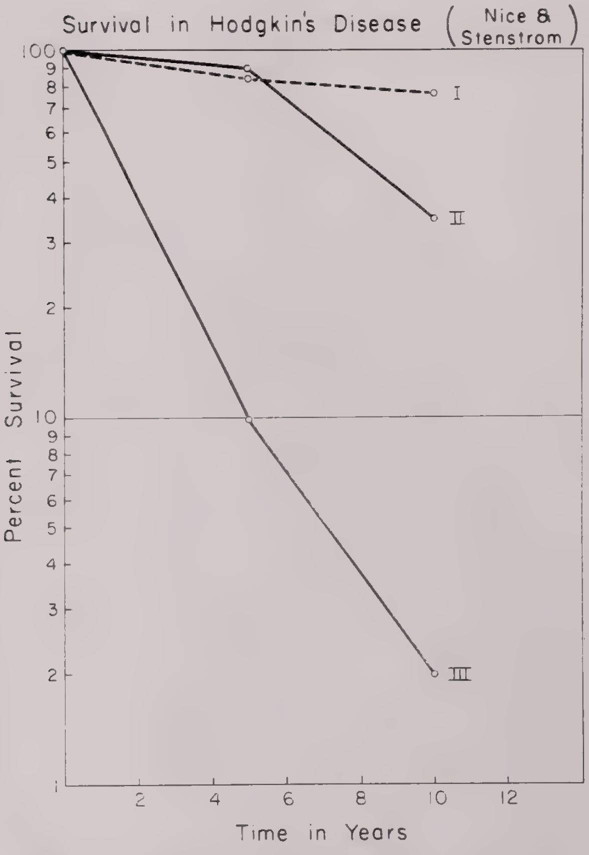

Fig. 3—Survival curve for Hodgkin's disease as a function of stage of disease based on older Peters[4] classification. Extent of disease (stage) correlates with survival following radiation therapy (from Nice and Stenstrom).

If the localized disease is in the upper half of the body, Kaplan[9] advocates treating essentially all the supradiaphragmatic nodes (mastoid, cervical, supraclavicular, mediastinal, and axilla) in a single field ("mantle") with the same therapeutic dose. The efficacy of this approach for Stage I disease is presently being compared with the localized field approach in a randomized national study which should in time provide additional relevant information. In Stage II (supradiaphragmatic) disease, the "mantle" approach is undoubtedly the most satisfactory form of therapy.

If localized disease appears below the diaphragm, an inverted "Y"-shaped field is used to treat all subdiaphragmatic nodes. Fields are shown in Figure 4. The therapy is directed to the entire para-aortic, iliac-pelvic, and groin nodes. Treatment of the stomach, spleen or retroperitoneum should also include appropriate adjacent regions and is best guided by chest radiography, lymphangiography, IVP and, if necessary, abdominal exploration. Whether to irradiate, or to remove the spleen surgically for subdiaphragmatic disease is still an open question.

Stage III disease and its proper management is presently highly controversial and under active investigation. Staging of early cases by means of lymphangioadenography permits early diagnosis, and megavoltage equipment facilitates aggressive and wide-field, high-dose radiation therapy. The general view has been well stated by Aisenberg of the Massachusetts General Hospital: "Radiation should not be withheld if the known disease can be encompassed within reasonable treatment fields." Since it had been shown that Hodgkin's disease is curable by radiation,[10] such a view is entirely a reasonable one, especially if the patient lacks constitutional symptoms, and provided his physical constitution would appear to tolerate the treatments. Although the feeling in the past had favored chemotherapy, recent experience reported by Kaplan[11] indicates that the disease-free period may be much increased if radiotherapy is directed to the entire supra- and infradiaphragmatic lymph node regions. The final answer to this approach will await further clinical experience and results from randomized clinical trials.

The efficacy of radiation for Hodgkin's disease is illustrated by representative examples described below.

Case Reports

Case 1

An example of a prolonged disease-free period following radiation therapy. A 37-year-old white male was found to have right supraclavicular adenopathy in 1949. No symptoms of fever, itch or night sweats were noted. Chest x-ray was normal and no additional adenopathy was noted (Stage I A). Radiation therapy was given to the entire right neck to a dose of 2,000 rad in two weeks time. At the present time, 20 years later, he is alive and remains free of evidence of disease.

Case 2

An example of a prolonged disease-free period following radiotherapy of recurrent disease. A 23-year-old white female presented in 1943 with mediastinal and left supraclavicular adenopathy (Stage II A). After radiation therapy the disease sites regressed completely (3500 rad/3 weeks). Twelve years later in 1955 she appeared with a 3 cm submental node and a mediastinal recurrence by x-ray. The mediastinum was re-treated and the submental node treated with x-rays. Both cleared completely. In 1968 she is well and remains free of evidence of disease (25 years), but was recently diagnosed to have peripheral neuropathy secondary to her prior radiotherapy.[12]

Even under circumstances where the disease is advanced (Stage IV) and hope of cure is

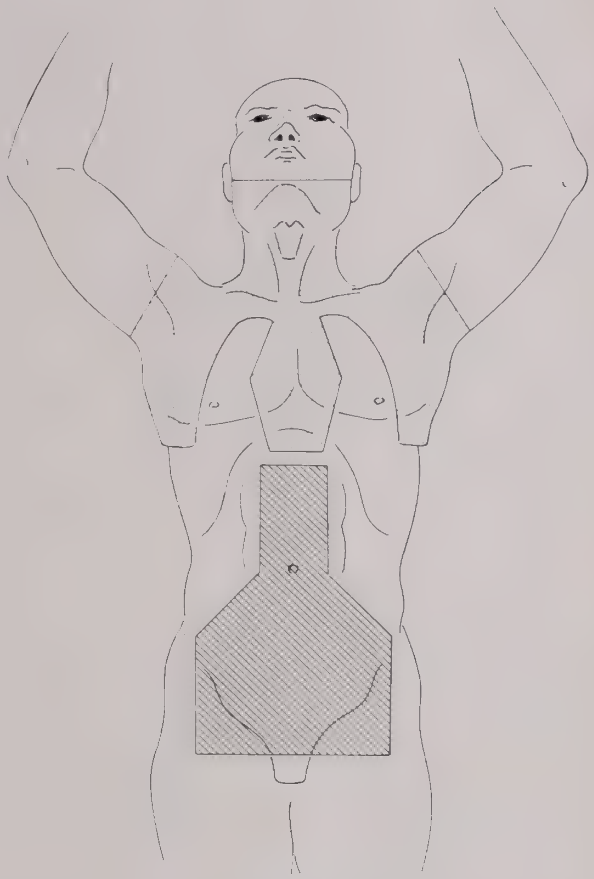

Fig. 4—Treatment fields presently advocated for radiotherapy of Hodgkin's disease. Upper shaded field ("mantle"), lower shaded field, or both may be treated, depending on stage of disease. The spleen may also be included in the lower mantle.

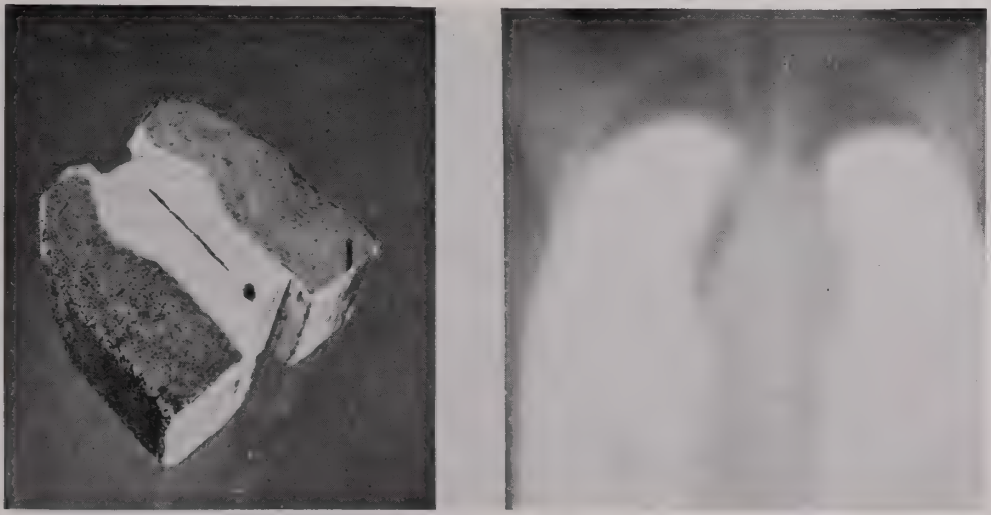

Fig. 5—Individualized lung shields are made for each patient treated to the supradiaphragmatic field (left). The protected regions are evident on the port radiograph routinely obtained on every patient treated (right). The lung shields are made in polyethylene cutout molds in which lead shot is embedded in Rigidax compound (method of Maruyama, Moore, Burns, and Hilger).

slim, radiation by virtue of its efficacy against local deposits represents a therapeutic modality which may be applied effectively at any time in the disease. Thus, while chemotherapy is necessary to control systemic symptoms, radiation by small-field techniques may be used for palliation of even advanced stages of the disease. Examples include:

1. Symptomatic adenopathy.
2. Superior vena caval or mediastinal obstruction.
3. Spinal compression (done carefully, this may spare a patient a surgical laminectomy).
4. Unhealing ulcerations.
5. Extranodal masses.
6. Symptomatic hepatosplenomegaly.
7. Pulmonary infiltration.

Case 3—Mass, Cranial Nerve Palsy and Unhealing Ulcerations Associated with Adenopathy in Advanced Disease.

A 53-year-old white male had known Hodgkin's disease of five years' duration. He had received many courses of x-ray therapy to small fields. However, there was progression of his disease and he was referred to the University Hospitals with advanced disease. He had a left temporal mass, and a large 8 x 8 x 4 cm mass of matted nodes in the right groin. Four courses of chemotherapeutic agents were attempted over a period of several months. Temporary response followed each course but was followed in turn by regrowth and progression. The right groin mass became secondarily infected and required incision and drainage. The incision site subsequently failed to heal, fungated through the skin, drained continuously, and progressively enlarged.

The patient then developed obstructive lymphedema of the right foot and leg. The left temporal mass extended to involve the left orbit with a resultant VIth cranial nerve palsy and diplopia. At this point radiation therapy was considered. Treatment of the right groin and pelvis and of the left temporal-orbital region was recommended and carried out with Cobalt 60 and localized beam therapy. In both sites, mass regression was evident after four to five treatments and complete regression was ultimately produced. The ulcerative groin mass healed completely and the left temporal mass regressed entirely, with restoration of normal eye motion and of normal vision.

Although the patient ultimately expired from advanced disease, these distressing symptoms were effectively and completely ameliorated.

Case 4—Therapy of Spinal Compression in Advanced Disease.

A 36-year-old white female was diagnosed with Hodgkin's disease in 1956 when she appeared with anemia, pruritus and left cervical adenopathy. Biopsy of the cervical nodes established the diagnosis. Over the next several years it became apparent that her disease was widespread. Multiple courses of various chemotherapeutic drugs, steroids and localized field radiotherapy maintained her symptom-free.

In 1967 she appeared, complaining of excruciating lumbar back pain. Diagnostic x-rays revealed osteolytic lesions of the vertebral bodies of D 12 and L 1. Physical examination showed hypalgesia of the lower extremities and depressed deep tendon reflexes. A sensory level was noted at the D 12 level. Some decrease in anal sphincter tone was present although bladder and bowel control were intact. The patient refused myelograms and surgery. Therefore, Cobalt 60 treatments were cautiously and deliberately delivered to the lumbodorsal region concurrently with large doses of steroids. About ten treatments and 2500 rad led to complete relief of back pain, restoration of normal neurological status, and reossification of the bone lesions. Two years later she is active and symptom-free and does her own housework for her family. No laminectomy was necessary.

Case 5—Mass, Leg Edema, and Blocked Urinary Tract in Advanced Disease.

A 71-year-old white male was found to have left leg edema. Admission evaluation disclosed several small nodes in the left neck and a matted 3 x 4 cm left inguinal mass. Biopsy of the left neck nodes disclosed Hodgkin's disease. Lymphangiography disclosed blocked lymphatics on the left side with abnormal periaortic nodes. An intravenous pyelogram was normal at this evaluation. He was considered Stage III A disease. Chemotherapy was started and a course of oral drugs given. Initial partial response was followed by marked regrowth and progression three months later. He was therefore admitted to the hospital and intravenous alkylating agents were given in high dosage. Again partial response was followed in two months by regrowth. Continuous oral cytotoxic therapy was therefore administered and was followed by incomplete regression.

During this time left leg edema (2^+ - 3^+ pitting) was continuously present. The left groin nodes were 3 x 3 x 5 cm in size. During this time a large left iliac fossa mass became apparent as well as partial blockage of the left urinary tract by intravenous pyelogram. At this point, radiotherapy consultation was requested. Treatment of the left groin, left iliac and para-aortic chain led to complete regression of the adenopathy and masses. Urinary tract obstruction was relieved and the left leg edema cleared. The patient eventually expired from advanced disease, but no further problems with leg edema, left inguinal nodes or the urinary tract ensued during his subsequent clinical course. The recent experience of Kaplan[11] with Stage III A disease suggests that initial management should have been radiotherapeutic.

For Stage III B and IV, the aim is often not to cure, but to produce patient comfort. It is in this category that chemotherapy has been so effective in improving the general status of the patient with active disease, and it is undoubtedly responsible for the improved quality of survival in many patients. Here, the aim of management is to restore a sense of well-being and free the patient of systemic symptoms. Blood transfusions, antibiotics, and general supportive measures are essential. Careful judgment in the choice and use of chemotherapeutic agents can bring about gratifying periods of remission while avoiding undue bone marrow toxicity.

Localized field radiotherapy can be used for the management of localized, symptomatic areas. Because the deposits are radioresponsive, relatively few treatments are usually required to achieve the aim of effective amelioration of symptoms and patient comfort. Moreover, the duration of response of localized deposits to irradiation is often much longer than for chemotherapeutic agents, which may be of short duration.

Conclusions

The view that Hodgkin's disease is a relentless and incurable disease is incorrect and unduly pessimistic. Early-stage disease may be cured by radiotherapy; advanced disease may be managed by chemotherapy combined judiciously with radiotherapy to maintain patient comfort. Radiation therapy should be delivered by competent specialists with meticulous attention to detail in the early or 'A'-stage patients. Large individually tailored fields are presently recommended to achieve the aim of cure. Use of unwarranted chemotherapy in early stages may further depress an already impaired immunological reactivity and competence of patients with Hodgkin's disease. It may further limit the adequacy and dosage possible with later radiation therapy by reducing normal tissue tolerance. Accurate staging correlates well with prognosis; and intensive radiotherapy in early Stage I and II disease and probably III A disease is the treatment of choice. In advanced disease, radiation represents a powerful adjunct to a comprehensive chemotherapeutic-medical program to maintain patient well-being and comfort and to ameliorate symptomatology.

The evaluation of stage in Hodgkin's disease is essential to its correct management and should be carried out by physicians with an interest in the disease, making use of all available techniques for its full evaluation. Accurate diagnosis, staging and appropriate therapeutics have been shown to alter the course of a disease previously regarded as ultimately fatal to one now considered potentially curable by proper therapy.

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Derivatively Speaking

Ranula—from Latin *rana* (a frog)

WHAT'S YOUR DIAGNOSIS?

A 64-year-old white female, a known diabetic for eleven years, with a nephrotic syndrome secondary to Kimmelstiel-Wilson and atherosclerotic coronary heart disease, was admitted because of multiple medical problems. She had been in chronic heart failure for several years but reported increasing pedal edema over the past six weeks and recent shortness of breath. While sleeping or relaxing, she usually lay on her left side.

The pertinent physical-finding examination revealed a suspicious mass in the left breast. The breasts were pendulous, the left larger than the right. Bilateral axillary nodes were thought to be palpated, and thickening of the skin in the upper quadrant of the left breast was found by all examiners. Thus a mammogram was performed.

The pertinent laboratory findings revealed an alkaline phosphatase of 19 and 28; a liver scan demonstrated a slightly enlarged liver with no filling defects. The bromsulphthalein was 22.

The mammogram was interpreted as being normal on the right. On the left, marked thickening of the skin was seen to involve the entire breast, but no mass could be detected. Carcinoma of the breast was a major consideration (Figures 1A and B). The suspected diagnosis of inflammatory carcinoma could not be maintained due to the lack of clinical manifestations of inflammation in the breast. A metastatic bone survey was negative. A chest radiograph revealed an enlarged heart, with bilateral pleural effusion, secondary to failure (Figure 2).

What is your diagnosis? (See page 594.)

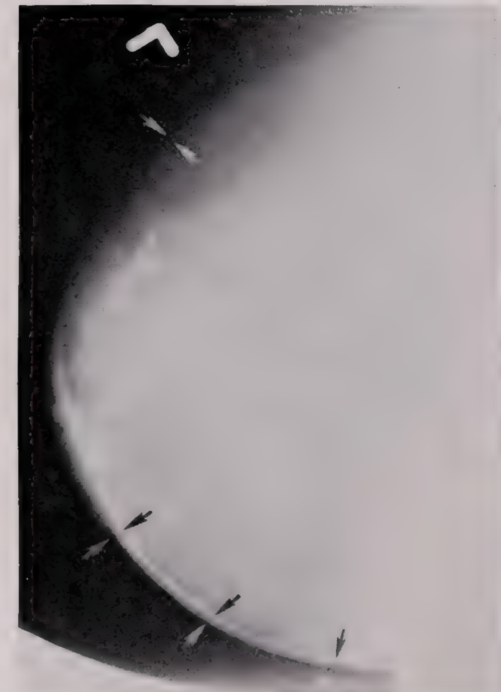

Fig. 1A—Mediolateral projection of the left breast demonstrating marked diffused skin thickening of the breast.

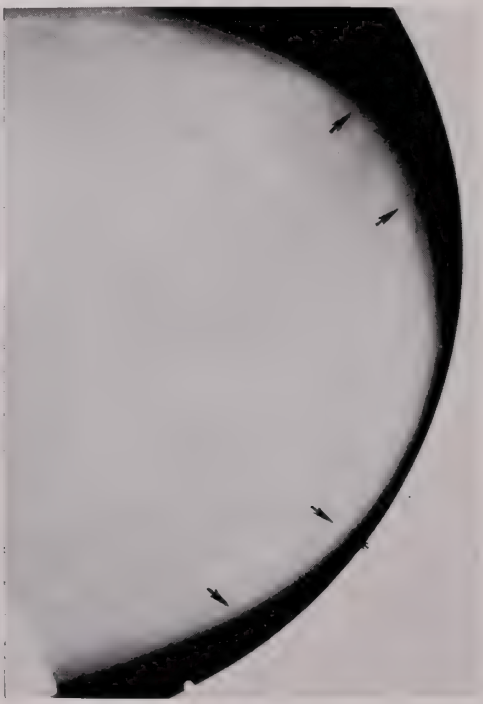

Fig. 1B—Craniocaudad projection of the left breast demonstrating with greater detail the skin thickening.

An Unusual "Complication" of A Duodenal Diverticulum

Report of A Case

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Sir William Osler[1] was the first to describe a duodenal diverticulum in the American literature in 1881. Since that time many series elucidating the surgical and pathologic aspects of this entity have been reported.

It has been stated[2] that almost any complication one could imagine has been reported with diverticula of the small bowel. This certainly holds true for duodenal diverticula, as exemplified by this brief case report.

Duodenal diverticula are found in approximately 1% of patients undergoing upper gastrointestinal x-ray examination.[3] About 95% of these diverticula are found on the concave aspect of the duodenal loop, usually in the second portion near the papilla of Vater, and most are of the extraluminal type.[2] This anatomic site is one of the factors resulting in the high operative mortality, which varies from 8 to 18%[2] in reported series. We could not find a complication such as ours recorded in the current literature.

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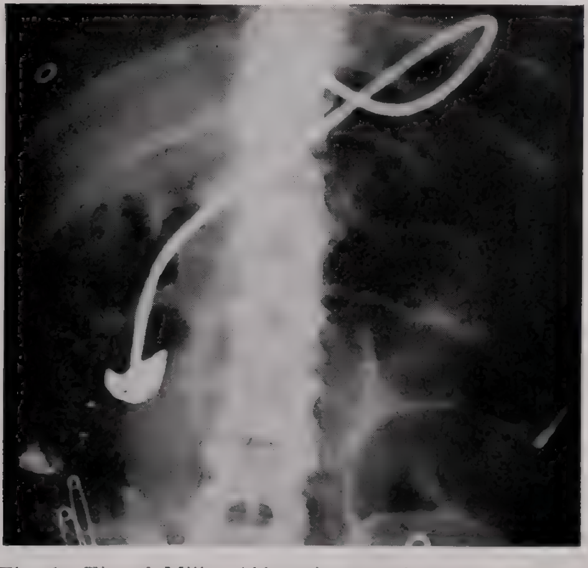

Fig. 1—Tip of Miller-Abbott in second portion of duodenum.

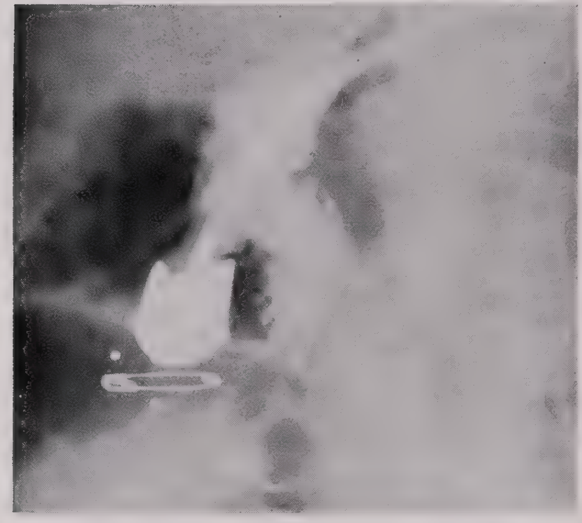

Fig. 2—Tip of Miller-Abbott tube lodged in duodenal diverticulum.

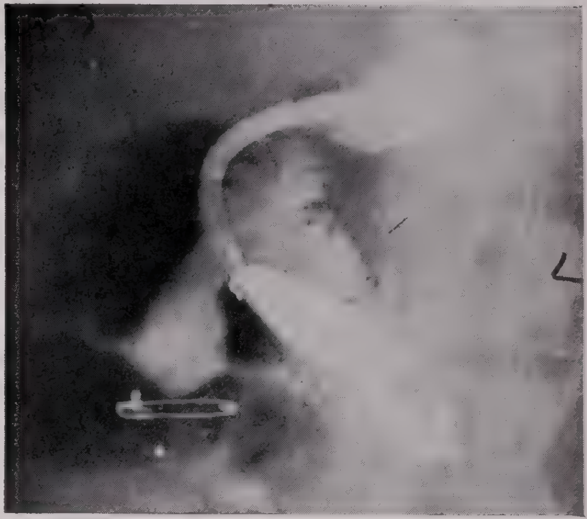

Fig. 3—Tube after manipulation, showing wide-necked duodenal diverticulum.

Report of Case

Recently a 67-year-old white man underwent routine cholecystectomy for cholelithiasis as well as excision of an incidentally found Meckel's diverticulum of the ileum. Partial obstruction of the small bowel became clinically evident on the fifth postoperative day. As this was suspected to be due to a soft adhesion, we elected to pass a Miller-Abbott tube for intestinal decompression. Under fluoroscopy the tip of the tube was easily passed through the pylorus into the second portion of the duodenum. Despite repeated tube manipulation, the tip of the tube would not advance beyond this point even with good drainage over a period of 48 hours (Figure 1).

At this stage it was decided to inject 37% meglumine diatrizoate (Gastrografin) into the tube and visualize the position of the tip under fluoroscopy. When this was done the tip was found to be lodged firmly in a wide-necked duodenal diverticulum lying on the convex aspect of the second portion of the duodenum (Figure 2). With correct positioning and manipulation the tip was easily passed beyond this diverticulum, whence it rapidly progressed distally (Figure 3). After decompression the tube was removed and the subsequent hospital course and convalescence were uneventful. As is our practice, we did not advise surgical removal of this diverticulum.

Summary

A patient had an asymptomatic and unsuspected diverticulum on the lateral (convex) portion of the second part of the duodenum. A Miller-Abbott tube became lodged in this diverticulum and caused a temporary diagnostic dilemma because of its failure to progress further.

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Harley Street

Every year the Medical Directory undertakes a counting of heads, and according to the current account there are 789 doctors with Harley Street addresses. To paraphrase Edsel Ford's after-dinner speech when the ten-millionth Ford rolled off the production line, "Whichever way you look at it, 789 is a lot of doctors." The lot includes forty-two women, one lord, fourteen knights, and twenty-three hyphenated names. The current range is from Abel to Zezi and includes, democratically enough, a Smith, a Jones, and a Robinson. You can pay your money and take your pick, and, unless you choose one of the three or four complete outsiders, you will have available to you all the resources of the best of British medicine, which is still better medicine than is practiced anywhere else in the world.*

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*Harvey Graham: A Doctor's London, 1952.

Mediastinoscopy

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MEDIASTINOSCOPY is a method of exploring the superior mediastinum with minimal surgical trauma. It provides a means for direct vision, palpation and biopsy of mediastinal lymph nodes and the other tissues of the mediastinum for diagnosis and prognosis. With mediastinoscopy, information about the nature and extent of many diseases of the lung and mediastinum can often be obtained without resorting to exploratory thoracotomy.

Mediastinoscopy was first introduced in Sweden in 1959 by Carlens.[1] It was not until 1966 that we began to occasionally utilize it; but as our experience increased and we learned its value, our indications for the procedure broadened. We now employ the technique with increasing frequency; as of May 1968 we have used it in 100 cases, 80 of them during the past year. This report presents a review of the technique of mediastinoscopy as we use it and the results.

Technique of Mediastinoscopy

Mediastinoscopy is carried out under general anesthesia with endotracheal intubation. The patient is positioned supine with his neck slightly hyperextended over a pillow beneath his shoulders. The anesthetist assumes his place at the side of the table while the surgeon works from the head of the table as in bronchoscopy.

Through a curvilinear incision of three or four centimeters in the suprasternal notch, the skin and platysma are divided (Figure 1). The strap muscles are separated longitudinally by dividing the fascial layer between them. The dissection is then carried through the pretracheal fascia and extended beneath it to and beyond the tracheal bifurcation, exposing the anterior and lateral walls of the trachea and both main bronchi. This dissection is performed digitally with the index finger (Fig-

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*Correspondent.

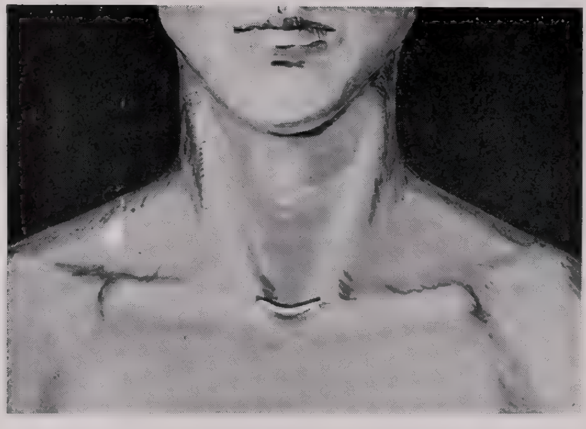

Fig. 1—Line of incision for mediastinoscopy.

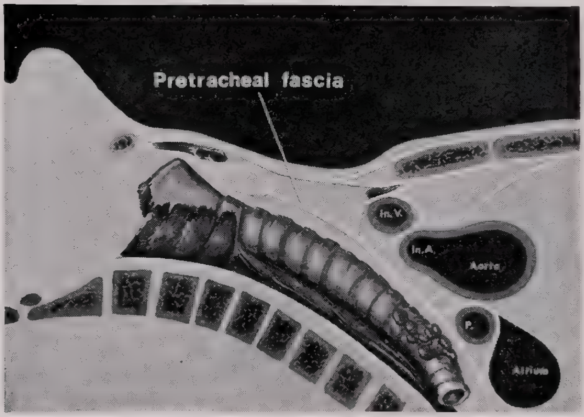

Fig. 2—Sagittal section of superior mediastinum.
In.V. = innominate vein
P.A. = pulmonary artery
In.A. = innominate artery

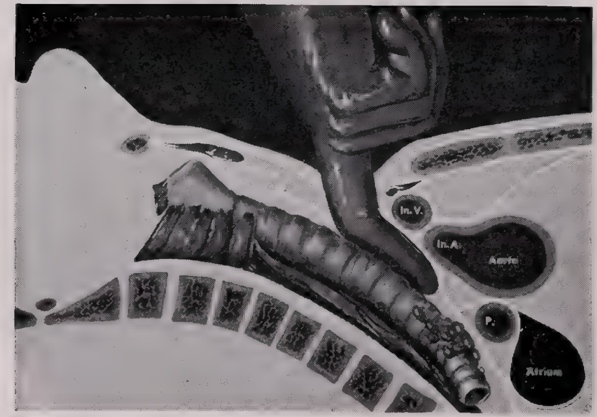

Fig. 3—Digital dissection down behind the pretracheal fascia.

ures 2 and 3). The aorta and innominate artery can be palpated anteriorly. Posteriorly the trachea and lymph node areas along each side of the trachea are felt (Figure 4). Palpation also gives valuable information about the consistency of the upper lobes and presence of tumor in the adjacent areas of lung and mediastinum which are useful in determining the sites for biopsy.

The mediastinoscope* is then introduced behind the pretrachea fascia and advanced to the carina, inspecting each side of the trachea, the carina, and the right and left main bronchi for two or three centimeters from their origins (Figures 5 and 6). The subcarinal region and the proximal portions of each bronchus may be freed from further areolar tissue with the help of blunt dissection with a long biopsy or dissection forceps.† Approaching the subcarinal nodes over the left bronchus avoids injury to the azygos vein. The lymph nodes are first freed from their surrounding tissues and then excised or biopsied. If there is any doubt as to the nature of tissues, as in differentiating the lymph nodes from vascular structures, a test puncture with a long 20-gauge needle may be performed. Large nodes, especially those encountered in sarcoidosis, can be enucleated with the finger. If no lymph nodes are identified, biopsy of mediastinal connective tissue is advisable. It is advisable to explore both sides of the trachea and carina, both for diagnosis and to determine the extent of the lesion. Closure of the wound is effected by catgut stitches for the muscle layers and subcuticular stitches for the skin.

Selection

In this series, selection of patients for mediastinoscopy has been prompted by the presence of pulmonary or mediastinal lesions suggestive of primary or metastatic cancer of the lung, or by hilar or mediastinal changes suggestive of granulomatous or lymphomatous involvement. Mediastinoscopy in these patients was usually done following exhaustive studies including routine radiography, tomography, bronchoscopy and bronchography. Bronchial washings were obtained at all bronchoscopies, and bronchial biopsies were made of all sus-

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*Made by Medical Products Co., distributed by V. Mueller Co.
†Pilling Company.

pected areas. Many patients had scalene node biopsies. When these were non-diagnostic, mediastinoscopy was then performed as the final step before undertaking exploratory thoracotomy for definitive diagnosis. In two patients where bronchial biopsies were positive, mediastinoscopy was performed to determine the extent of the lesion for prognostic information.

Contraindication for mediastinoscopy was evident in only one patient not included in this series. This patient had a metastatic lesion involving the fifth cervical vertebra and could not extend his neck. Therefore, Harken's[2] procedure under local anesthesia was performed, establishing the diagnosis in this patient.

Results

Mediastinoscopy was performed on 100 patients, aged from seven to 82 years. The majority were between 50 and 70 years old (Table 1).

TABLE I

Mediastinoscopy & Mediastinal Lymph Node Biopsy
Age and Sex Distribution

Age in Years	Men	Women	Total
0-9	1		1
10-19	1		1
20-29	4	2	6
30-39	4	1	5
40-49	10	5	15
50-59	17	6	23
60-69	28	5	33
70-79	11	4	15
80-89		1	1
Total	76	24	100

Forty patients had benign lesions, the remaining 60 malignant ones.

Benign Lesions

Thirty-four of 40 patients (85%) yielded positive findings at mediastinoscopy (Table 2). Eighteen of these 40 yielded mediastinal lymph nodes diagnostic of sarcoidosis. In 10 of these 18 patients prior scalene node biopsies had been performed with negative results; eight patients had not had scalene node biopsies. Thus with mediastinoscopy, all of the 18 patients had positive findings for sarcoidosis.

Nineteen patients had mediastinal lymph nodes which were interpreted on microscopic examination as normal or showing benign

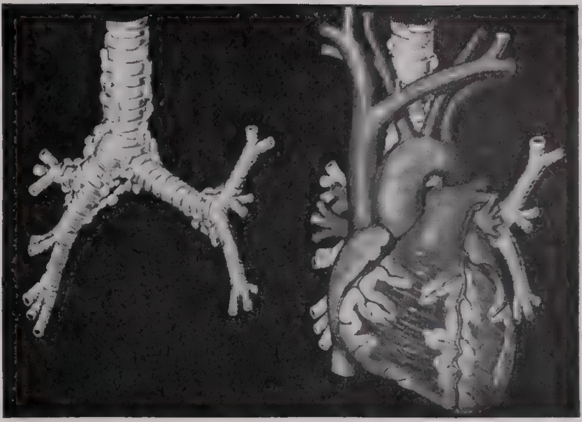

Fig. 4—Relation of mediastinal structures.

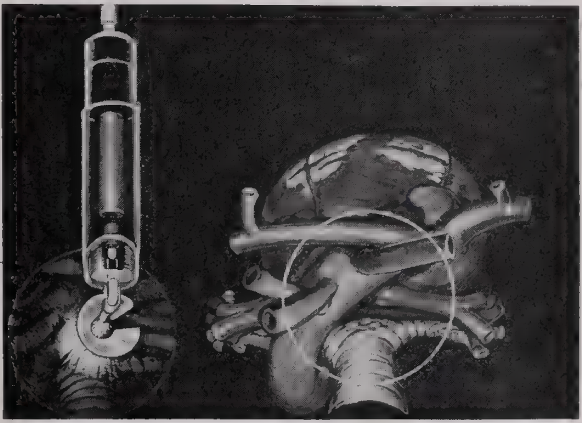

Fig. 5—Mediastinoscopic view of mediastinal structures.

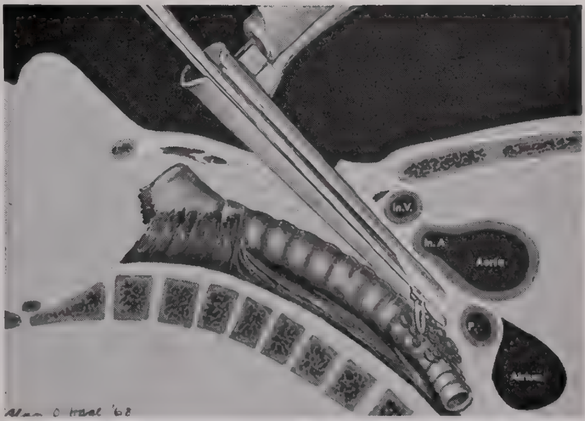

Fig. 6—Introduction of mediastinoscope and biopsy mediastinal lymph nodes.

TABLE 2
Mediastinoscopy—Results—Benign

Final Diagnosis	No. of Patients	Positive Mediastinoscopy
Benign:		
Sarcoidosis	18	18
Inflammatory	19	15*
Lipoma (mediastinum, chest wall)	2	
Vascular anomaly	1	1
Total	40	34

*Represents cases which proved to have inflammatory lesions at thoracotomy and in retrospect corresponded to findings at mediastinoscopy.

TABLE 3
Mediastinoscopy—Results—Malignant

Final Diagnosis	No. of Patients	Positive Mediastinoscopy
Malignant:		
Primary carcinoma in lung	51	30
Metastatic carcinoma from:		
Breast	2	2
Kidney	2	2
Undetermined origin	1	
Sarcoma chest wall	1	
Reticulum cell sarcoma	2	2
Hodgkin's sarcoma	1	1
Total	60	37

TABLE 4
Yield of Diagnostic Procedures Used on 51 Patients Who Ultimately Proved to Have Cancer of the Lung

	No. Done	Tissue Diagnosis
X-ray	8	
Tomogram	6	
Bronchoscopy & bronchograms	38	
Bronchial biopsy	2	2
Bronchial washings	38	12
Sputum	14	5
Scalene node biopsy	13	0
Bone rib biopsy	4	4
Mediastinoscopy	51	30
Exploratory thoracotomy	15	15

hyperplasia or nonspecific granulomatous reactions. Fifteen of these patients underwent thoracotomy, at which time they proved to have either non-specific granuloma, chronic infections or bronchiectasis with secondary chronic peribronchial lymphatic hyperplasia. In these patients mediastinoscopic findings correlated with thoracotomy findings. Two large lesions, one involving the anterior mediastinum and the other involving a peripheral subpleural location in the chest wall, proved to be lipomas at thoracotomy. In each, mediastinoscopy was negative.

One child with a mediastinal mass proved to have a vascular anomaly at mediastinoscopy, accounting for the x-ray picture suggesting tumor of the mediastinum.

Malignant Lesions

Sixty of the 100 patients studied had malignant lesions (Table 3). Fifty-one had primary cancer of the lung, five had metastatic lesions and four had lesions of lymphomatous origin.

In the 51 patients who ultimately proved to have cancer of the lung, 30 had positive findings at mediastinoscopy. Fifteen patients in this group had negative mediastinal lymph nodes at mediastinoscopy and were subjected to thoracotomy for diagnosis and treatment. In retrospect, another eight patients should have had positive nodes at mediastinoscopy, as thoracotomy revealed lesions in the mediastinal nodes within the reach of the mediastinoscope. From the anatomical evidence in these cases, it appears that the correct diagnosis could have been established in 38 of the 51 patients (by mediastinoscopy) or 74.5 percent.

All of these patients have had various diagnostic procedures as indicated in Table 4. It is interesting that of the 38 patients in this group who were bronchoscoped, only two had lesions amenable to bronchial biopsy which were diagnostic. In these two patients, mediastinoscopy was performed to determine the extent of the spread to mediastinal lymph nodes. However, these 38 patients who also had mediastinoscopy do not represent all the cases bronchoscoped. Those whose lesions were diagnosed by bronchoscopy alone are not included in this report; therefore these 38 patients represent a select group.

Bronchial washings were obtained in all of these 38 patients at bronchoscopy and were positive in 12. Positive bronchial washings were usually accepted as supportive but not considered as definite evidence of tumor.

Expectorated sputa were examined for malignant cells in 14 of these patients. In five they were reported as "atypical" or "suspicious." In two of these, mediastinoscopy was negative. Yet because of the patient's history and chest roentgen findings and clinical deterioration, carcinoma was accepted as the most likely diagnosis without thoracostomy.*

Four patients who had negative nodes on mediastinoscopy were discovered to have bone lesions, one in the iliac bone, three in the ribs. These were biopsied and metastatic carcinoma was found. Procedures which determined final diagnosis of cancer of the lung in 51 patients are summarized in Table 5.

It is interesting to compare three patients in whom carcinomatous nodes were found by mediastinoscopy and who were nevertheless subjected to thoracotomy with those who had negative mediastinoscopy and were subjected to thoracotomy. Two of the three patients with positive mediastinoscopy who were operated on were young, and the chest x-rays suggested that the lesions could be resected; while in the third case the thoracotomy was attempted despite the carcinomatous mediastinal lymph nodes to control infection in a cavitating cancer.

All three were found non-resectable because of tumor invasion of either the aorta, pulmonary artery or veins (Table 6).

Discussion

Mediastinoscopy is a simple and safe method of exploring the superior anterior mediastinum for diagnostic and prognostic purposes.

In this series, 30 of 51 cases of cancer of the lung were diagnosed and evaluated as non-resectable by mediastinoscopy; thoracotomy was thus avoided. In six additional cases, pelvic bone or rib biopsy or examination of sputa gave the final diagnosis and evaluation, although mediastinoscopy had failed to find malignant tissue. Positive mediastinoscopy in malignant disease usually signifies a poor prognosis. Patients with such findings are generally past the stage where they can be considered for curative resection. The presence of metastatic nodes along the trachea or direct invasion of the mediastinum with the tumor precludes curative resection in most cases.[3]

This is illustrated in the three patients who had positive mediastinoscopy and were subjected to thoracotomy because the outlook seemed favorable, yet all were found to be non-resectable. On the other hand, of the 15 patients with negative mediastinal lymph nodes, nine were found resectable at thoracotomy. This would indicate a 60 percent "resectability for cure" rate in otherwise favorable patients found free of mediastinal involvement by mediastinoscopy.

The follow-up on 27 patients with positive mediastinal nodes not subjected to thoracotomy did indeed suggest that the lesions would have been non-resectable by the very short downhill course that followed their diagnosis, despite irradiation or chemotherapy in some.

Summary and Conclusion

Technique of mediastinoscopy is reviewed and the results in our first 100 patients presented. There were no complications. Mediastinoscopy is a valuable adjunct for diagnosis and prognosis of lesions involving the mediastinal structure. In many cases, it provides information otherwise available only by thoracotomy.

TABLE 5

Procedures Which Determined Final Diagnosis of Cancer of the Lung in 51 Patients

Mediastinoscopy	28
Bronchial biopsy	2*
Exploratory thoracotomy	15
Rib or bone biopsy	4
Sputum	2

*Mediastinoscopy was also positive.

TABLE 6

Thoracotomy Done Despite Positive Mediastinoscopy (Three Patients)

One had small cell carcinoma.
One had adenocarcinoma with invasion of mediastinum.
One had squamous cell carcinoma with abscess cavities.
All were non-resectable at thoracotomy.

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*See Test Your Word Score Page 672.

In this series, exploratory thoracotomies for diagnosis were avoided in 18 of 18 patients with sarcoidosis. When all the benign lesions in this series are considered, exploratory thoracotomies were avoided in 23 of 40 (57.5 percent). As for malignant lesions, thoracotomies were avoided in 34 of 51 patients (not including those three who had thoracotomy despite positive mediastinoscopy), or 66.6 percent.

Addendum

Since submission of this paper our experience with an additional 40 cases supports the above conclusions.

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Highway Safety

Doctors who care for the human wreckage from highway carnage know that positive steps are called for right now. A systems approach can be designed to cut in half today's mortality rate and to significantly reduce crippling injuries. The subsystems in this approach involve the *Driver,* the *Automobile,* and the *Medical Care.*

The Driver must be conditioned to slip into his safety harness every time he enters his auto—without fail. We know that wearing a seat belt has reduced accident mortality by 40 percent, and wearing a shoulder harness adds another 30 percent to probability of survival.

The drinking driver must be eliminated. If he will not assume responsibility, he must be subject to increasingly severe penalties under the law. The favorable Supreme Court decision on "stop and frisk" by police officers should have a salutary effect by permitting them to investigate suspects under reduced liability to themselves.

The Automobile manufacturers must continue improvement of vehicular crash design. This calls for universal energy-absorbing devices, such as collapsible steering gears, bumpers which give, and padded instrument panels. An improved shatterproof glass is now found on many cars—better than standard safety glass but not perfect as yet. Car frames should be strengthened, featuring impact protection from the sides as well as from the front and back.

Effective Medical Care requires rapid transport of accident victims. The mortality rate rises rapidly for each half-hour delay in serious accidents. Helicopters or medicopters should be considered for urban areas where rush hour traffic seriously hampers accessibility by ambulance.

A trauma unit should be included in all major medical centers. Although few trauma units exist currently, they hopefully will become as effective and common as recovery rooms. Such a special facility dictates responsive training of physicians and supporting personnel. Trauma patient care should be recognized as a subspecialty in its own right with careful attention paid to proper training of doctors, nurses, and technicians.

Taken as a total system—subject to concerted and continuing promotion—these three approaches could be expected to improve considerably the current intolerable record of U.S. highway safety.

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Infarct of the Prostate Causing Pyohydronephrosis*

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INFARCTION OF THE prostate is a well recognized entity; the diagnosis is usually made at autopsy or on sectioning the surgical specimen. Frequently there is no history to suggest any significant sequelae, but there are numerous reports of acute urinary retention secondary to prostatic infarction. An unusual complication of prostatic infarction is presented.

Case History

History and Physical Examination

A 73-year-old white male was transferred to the Minneapolis Veteran's Administration Hospital on December 7, 1967, because of anuria of two days' duration. He had previously been admitted to another hospital because of several syncopal episodes. He had last voided just prior to leaving for that hospital. Treatment had included intravenous fluids and intramuscular penicillin. There had been no abdominal or flank pain during this period and he denied voiding symptoms.

Past history included bilateral renal calculi since 1924, with a right nephrectomy in 1962. Apparently a left renal calculus had been present at that time. An enterocolostomy had been performed because of regional enteritis.

Examination revealed a lethargic elderly male in no distress and with no complaints. Blood pressure was 126/58 mm. Hg., pulse 96/min., and temperature 103 degrees (rectal). There was guarding in the left upper quadrant and mild left flank tenderness. The surgical scars were noted. The prostate was 2 plus enlarged with a firm rubbery consistency; it was not tender.

Laboratory Data

Initial laboratory data were: hemoglobin 10.5 gm.%, WBC 13,700 with 92% neutrophiles, BUN 58 mgm.%, sodium 129 mEq./L, chlorides 97 mEq./L, potassium 4.6 mEq./L, CO_2 combining power 19.5 mEq./L. KUB x-ray showed a staghorn calculus involving the left upper pole.

Hospital Course

Cytoscopy revealed a 5-cm.-long prostatic urethra with hyperemic mucosa and enlarged obstructing lateral lobes. The bladder mucosa showed evident cystitis. The left side of the trigone was elevated and edematous, and the left ureteral orifice was lateral to the expected position. No efflux‡ occurred. A #5 Fr. ureteral catheter was passed to 25 cm. and 30 cc. of purulent material was aspirated. A pyelogram showed the staghorn calculus and hydronephrosis (Figure 1). The renal pelvis was irrigated with neo-

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*See Editorial Page 601.

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‡See Test Your Word Score Page 672.

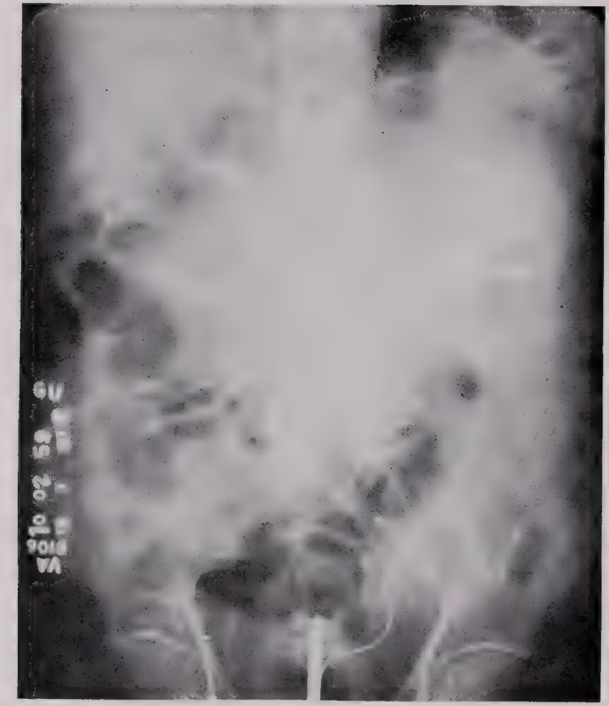

Fig. 1—Pyelogram after aspiration of 30 cc. pus.

mycin solution and the catheter left indwelling. Urine culture failed to grow any bacteria.

Treatment with intravenous Keflin and chloromycetin was started and the ureteral catheter irrigated with 1% neomycin solution every two hours. Because of repeated obstruction of the catheter by debris, a second catheter was passed on December 8, 1967. A withdrawal pyelogram showed complete filling of the ureter to the ureterovesical junction (Figure 2). The patient's temperature was normal on December 10, 1967, but because of intermittent obstruction of the catheters with recurrent fevers, a nephrostomy was performed two days later. His temperature became normal the following day. No attempt was made to remove the staghorn calculus which did not involve the lower pole calyx.

Five days after the nephrostomy the patient began to void small amounts of urine with a residual of 60 cc. A cine-pyelogram showed normal peristalsis along the entire ureter with complete emptying within 15 minutes. A sixteen-gram transurethral resection of the prostate was performed on December 29, 1967. The edema of the trigone was absent and the left ureteral orifice was in its normal position. During the resection the tissue from the posterior and apical areas of the left lobe was noted to be mottled dark brown. *This proved to be infarcted prostate.*

The nephrostomy tube was clamped and later removed, and the patient was voiding normally when discharged on January 8, 1968. In retrospect the changes at the trigone and orifice were secondary to the prostatic infarction and resulted in pyohydronephrosis. Acid phosphatase determinations had not been done because the infarct had not been suspected.

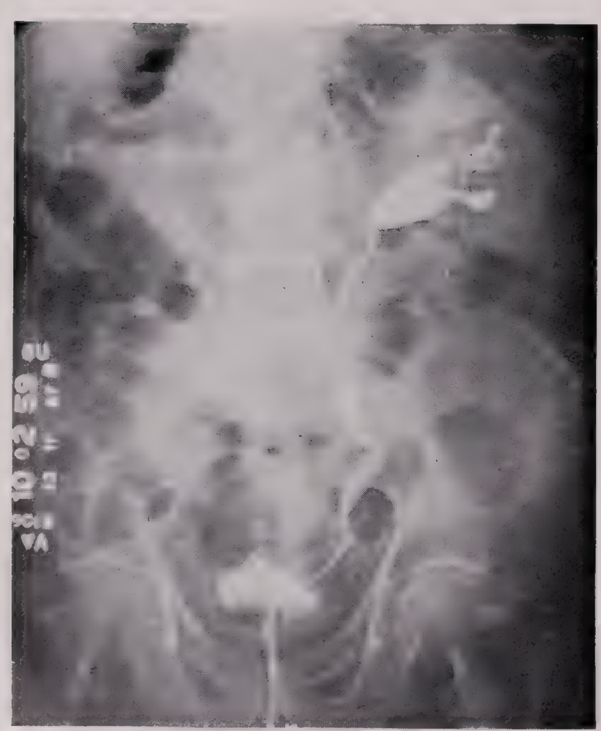

Fig. 2—Filling to ureterovesical junction on withdrawal of pyelogram.

Discussion

Since the report of Abeshouse in 1933,[1] which alerted urologists to this disease, there have been several papers dealing with prostatic infarction. From 8% to 25% of surgical or autopsy specimens have been found to contain areas of infarction.[3,8] Several causes have been proposed, including trauma (endoscopy, catheters, fecal impaction), infection, vascular compression by an adenoma within the relatively indistensible prostatic capsule, thrombosis of the periprostatic venous plexus, arteriosclerosis, and embolic phenomena.[6,7] Zufall reported a case of prostatic necrosis following repair of a ruptured aortic aneurysm.[10]

The usual clinical picture is that of prostatism, frequently with acute urinary retention. Some authors have described gross hematuria, but rarely is there any pain secondary to the infarct.[8]

The microscopic appearance of prostatic infarction is central infarction with peripheral hemorrhage and leucocytic infiltrate; later there is invasion by fibroblasts and new vessels and fibrosis.[4,7] Squamous metaplasia of surrounding acini is common and has been misinterpreted as adenocarcinoma of the prostate.[2,5] The only known biochemical change due to the infarction is transient elevation of the serum acid phosphatase.[9]

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Postcholecystectomy Syndrome

This syndrome is characterized by the persistence after gallbladder removal of preoperative symptoms or by the initial appearance of similar symptoms after biliary tract surgery. Repeated attacks of biliary colic, perhaps with abdominal pain, bloating, nausea, and vomiting, are characteristic. Jaundice, chills, and fever may also be present. An unnecessarily long cystic duct stump, mechanical irritation, stenosis or obstruction of the common bile duct because of stone or stricture, cholangitis, functional spasm and incoordination or fibrosis of the sphincter of Oddi, or traumatic neuromas may be causative.

Determination of the postoperative pathologic process is difficult even with the aid of intravenous cholangiography. McClenahan and associates, in applying this technique in a series of 121 patients with persisting postoperative symptoms, demonstrated common bile duct abnormalities in 33 percent of patients. Pathology included cystic duct remnants in 16.5 percent, calculi in 9.1 percent, and stricture in 7.4 percent. Quite significant was his control study of 46 postoperative asymptomatic patients. In this series disorders of the common bile duct were demonstrated in 34.8 percent, cystic duct remnants in 28.3 percent, calculi in 4.3 percent, and strictures in 2.2 percent. These contrasting figures indicate the difficulty of relating postcholecystectomy symptoms to demonstrable pathology in the lower biliary tract.

Differential diagnosis should exclude functional disorders with gastrointestinal manifestations and organic disease outside the biliary tract. Surgical exploration is frequently necessary to determine and correct the causal factor.

Durham, Robert H.—Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York

Tell the truth, and so puzzle and confound your adversaries.—Henry Wotton

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A pin has as much head as some authors, and a good deal more point.—George Prentice

Answer to What's Your Diagnosis?

(From page 582)

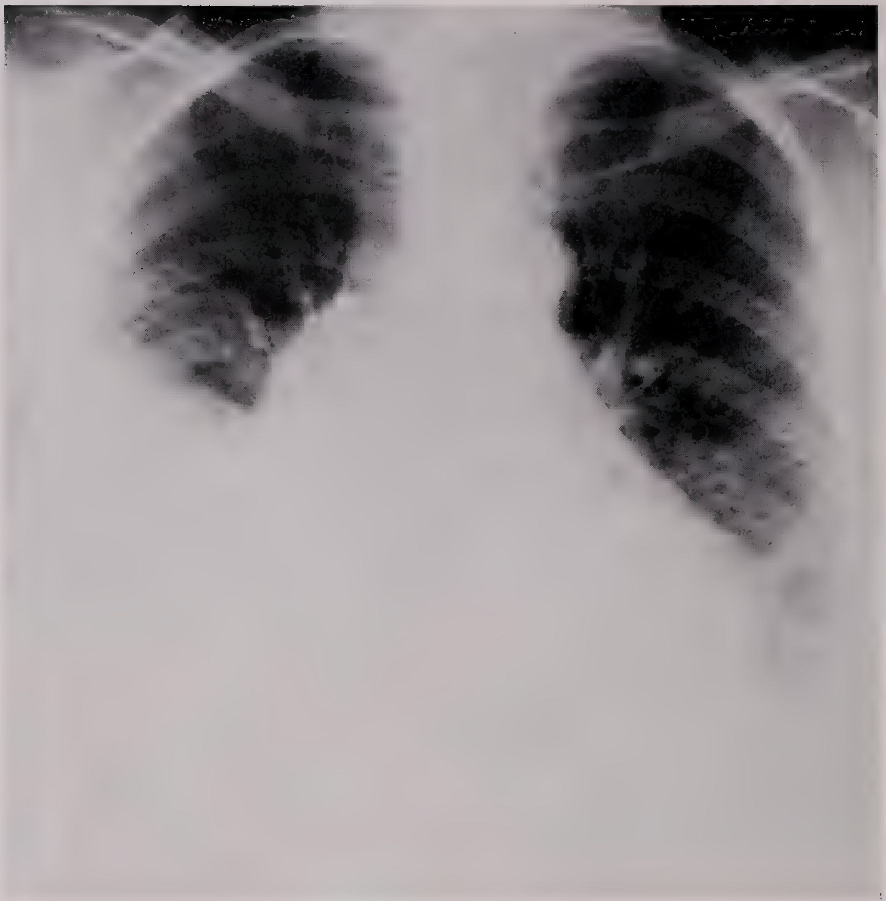

Fig. 2—Posteroanterior projection of the chest demonstrating bilateral pleural effusion due to cardiac failure.

The patient was treated with diuretics and bed rest, and lost 20 pounds in six days. With a decrease in the pedal edema, within 14 days the total weight loss was 43 pounds. The edema had disappeared completely.

A repeated mammogram revealed no thickening of the skin, and the major suspicion of carcinoma of the breast was abandoned. The alkaline phosphatase and the bromsulphthalein remained somewhat elevated, which was thought to be due to chronic, passive congestion.

It is now a well-known fact that early thickening of the skin is better evaluated radiographically than clinically.[2] The numerous etiologies for this occurrence have been described by Morrish.[3]

Harold A. Baltaxe, M.D.
Minneapolis, Minnesota

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An optimist is a girl who mistakes a bulge for a curve.—Ring Lardner

Thymoma with Myopathy

Report of A Case

JACQUES V. SOUADJIAN, M.D.*
LLEWELYN P. HOWELL, M.D.†
EDWARD H. LAMBERT, M.D.‡
Rochester, Minnesota

The role of the thymus in immunologic phenomena has recently been emphasized,[1] but the relationship between the thymus and autoimmune disorders is yet to be defined. There is suggestive evidence of an auto-immune mechanism in myasthenia gravis[2] and polymyositis[3]; remission of myasthenia gravis following thymectomy has been observed for years.[4,5] In 1964 Klein and colleagues[6] reported two patients with thymoma and polymyositis in whom the polymyositis remitted after treatment with glucogenic steroids; these patients developed clinical manifestations of myasthenia gravis soon after thymectomy. These authors suggest that there may be a relationship between myasthenia gravis and polymyositis—particularly in the presence of thymoma—on the basis of a common auto-immune mechanism in which thymic dysfunction plays a role. Others[7,8] have also suggested that there is a relationship between polymyositis and myasthenia gravis.

We are reporting a patient with thymoma and myopathy, in whom the myopathy decreased after thymectomy.

Report of Case

A 65-year-old farm wife and mother of five children came to the Mayo Clinic on December 14, 1964, on the advice of her physician who had discovered a mediastinal mass two weeks earlier. She had enjoyed good health all her life except for menorrhagia, which had been treated with intrauterine menopausal doses of radium in 1944, and varicose veins, which had been operated on in 1945. About the middle of October 1964 she requested a "flu shot" from her physician; this was given and, later the same day, she observed swelling in the arm that received the injection. Two days later, to the best of her recollection, she first noted swelling of her feet. Diuretics were prescribed without apparent benefit. She then began to have difficulty with phonation and swallowing, experienced feelings of "weakness and a little dizziness," and found that her "left little finger had curled up and the left hand felt stiff and tender."

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*Mayo Graduate School of Medicine (University of Minnesota), Rochester: Resident in Internal Medicine.

†Mayo Clinic and Mayo Foundation: Section of Medicine.

‡Mayo Clinic and Mayo Foundation: Section of Physiology.

Physical Findings

On examination the patient weighed 165 lb (usual weight 160 lb). She had moderate pitting edema over the ankles in the presence of some lipedema. There was evidence of increased pressure in the external and internal jugular and the subclavian veins on the left side, but there was no evidence of increased pressure in the veins on the right side or over the abdomen and legs. The edge of the liver was palpable; the lungs were clear. A puddling of mucus in the pyriform sinuses at the introitus of the esophagus was seen; the larynx appeared normal.

Motor Function Tests

Testing of motor function revealed mild generalized weakness, especially in the pelvic girdle muscles. In tests of esophageal motility the contractions in the pharynx, pharyngoesophageal region, and throughout almost all of the esophagus were feeble. This abnormality was similar to that previously seen in patients with dermatomyositis and scleroderma and with the myasthenic syndrome sometimes associated with bronchogenic carcinoma.

Electromyographic studies revealed numerous fibrillation potentials in many areas of all the muscles that were examined, including the left biceps brachii, first dorsal interosseus, anterior tibial, and vastus medialis. The motor-unit action potentials during voluntary contraction were numerous. They were predominantly short-duration spikes and polyphasic potentials, especially in areas with fibrillation. The mean duration of motor-unit action potentials in the biceps brachii was 6.5 msec (range 3 to 10 msec, $n = 22$): significantly below the range of mean values (9.3 to 14.1 msec) for seven healthy persons of the same age. Thirty-five percent of the motor-unit action potentials were polyphasic, in contrast to values of less than 10% in healthy persons. The amplitude of the summated muscle action potential evoked by a single maximal stimulus to the ulnar, median, or peroneal nerve was low (25 to 60% of the normal mean), but study of the effects of repetitive stimulation failed to reveal any evidence of a defect of neuromuscular transmission. Conduction velocities of motor fibers of the ulnar, median, and peroneal nerves between elbow and wrist or knee and ankle were normal (65, 58 and 58 m/sec, respectively). The latency (distal latency) of the muscle action potential evoked by a maximal stimulus to the nerve at the wrist or ankle was in each instance in the midpart of the normal range. The action potential of large afferent fibers of digital nerves had a normal amplitude (14 μv) and latency (2.8 msec to negative peak, distance 13.0 cm). The pattern of abnormalities in the electromyographic and nerve-conduction studies was that of a myopathy. It was consistent with a diagnosis of polymyositis but not pathognomonic for this disorder.

Transaminase Activity

The serum glutamic-oxalacetic transaminase activity (SGOT) was 1.97 μmoles/hr/ml (normal up to 1.43 μmoles/hr/ml) and the serum creatine kinase activity was 17.46 μmoles/hr/ml (normal up to 3.27 μmoles/hr/ml). X-ray examination disclosed, in the anterior mediastinum, a large mass that extended into the left lung field.

Operation

On December 21, 1964, a median sternotomy was performed and a thymoma measuring 9 by 6 by 5 cm was excised. This was predominantly of the lymphocytic type. A specimen of the pectoralis major obtained at the same time revealed more than the usual variation in the diameter of muscle fibers. There were a few widely scattered basophilic fibers with large vesicular nuclei. Several intrafascicular blood vessels were surrounded by excessive fibroblasts. There was no significant perivascular accumulation of round cells. The abnormalities were considered to be consistent with myopathy of a nonspecific type. Postoperatively the patient did well and her strength increased, although she continued to have some dysphagia and hoarseness. Eight days after operation the serum creatine kinase activity had decreased to 5.64 μmoles/hr/ml.

When the patient returned in June 1965, at our request, she professed to be well and weighed 150 lb. The pitting edema of her legs was decreased. On close inquiry she admitted to some persistent weakness, hoarseness, and dysphagia. The electromyogram showed a marked decrease of fibrillation in the muscles tested. Only rarely during the examination were fibrillation potentials observed; however, abnormalities of motor-unit action potentials were still present. Serum glutamic-oxalacetic transaminase activity was 0.86 μmole/hr/ml of serum and the creatine kinase activity was 3.05 μmoles/hr/ml of serum. A communication from her in May 1966 indicated that she was still doing well.

Comment and Summary

A patient presented evidence of a generalized myopathy;* she had dysphagia, with abnormal esophageal motility, and muscle weakness, especially of the pelvic girdle muscles; serum glutamic-oxalacetic transaminase and creatine kinase values were increased; and the electromyogram showed fibrillation in resting muscles, decreased duration of motor-unit potentials, and an increase in the proportion of polyphasic potentials. Muscle biopsy showed abnormal but nonspecific changes. On removal of the thymoma the patient's strength improved; serum glutamic-oxalacetic transaminase and serum creatine kinase values decreased to normal, and electromyography showed marked reduction in fibrillation. To our knowledge this is the first report of a patient with thymoma and myopathy whose symptoms and findings diminished after thymectomy. Spontaneous remissions in polymyositis have been reported, but in this patient the possibility that the remission was related to thymectomy cannot be excluded.

References may be secured from the author.
*See Test Your Word Score Page 672.

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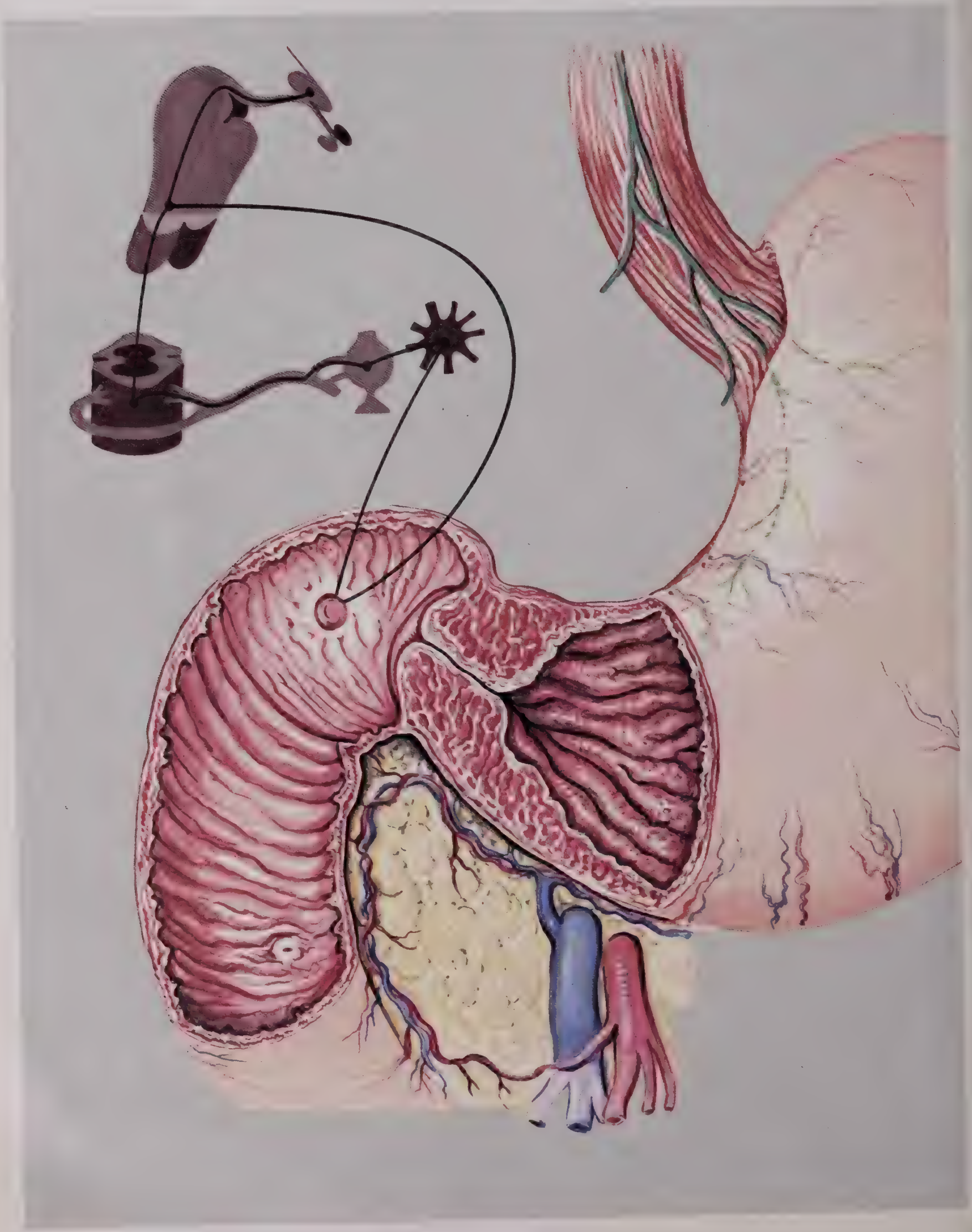
(1286M)

Healing the ulcer crater



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Therapeutic Activity—Pro-Banthīne blocks ulcerogenic impulses at both parasympathetic effector sites and ganglia and at sympathetic ganglia.

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Precautions: Since varying degrees of urinary hesitancy may occur in elderly men with prostatic hypertrophy, this should be watched for in such patients until they have gained some experience with the drug. Although never reported, theoretically a curare-like action may occur with possible loss of voluntary muscle control. Such patients should receive prompt and continuing artificial respiration until the drug effect has been exhausted.
Side Effects: The more common side effects, in order of incidence, are xerostomia, mydriasis, hesitancy of urination and gastric fullness.
Dosage: The maximal tolerated dosage is usually the most effective. For most adult patients this will be four to six 15-mg. tablets daily in divided doses. In severe conditions as many as two tablets four to six times daily may be required. Pro-Banthīne (brand of propantheline bromide) is supplied as tablets of 15 mg., as prolonged-acting tablets of 30 mg. and, for parenteral use, as serum-type vials of 30 mg. The parenteral dose should be adjusted to the patient's requirement and may be up to 30 mg. or more every six hours, intramuscularly or intravenously.

981 4/69

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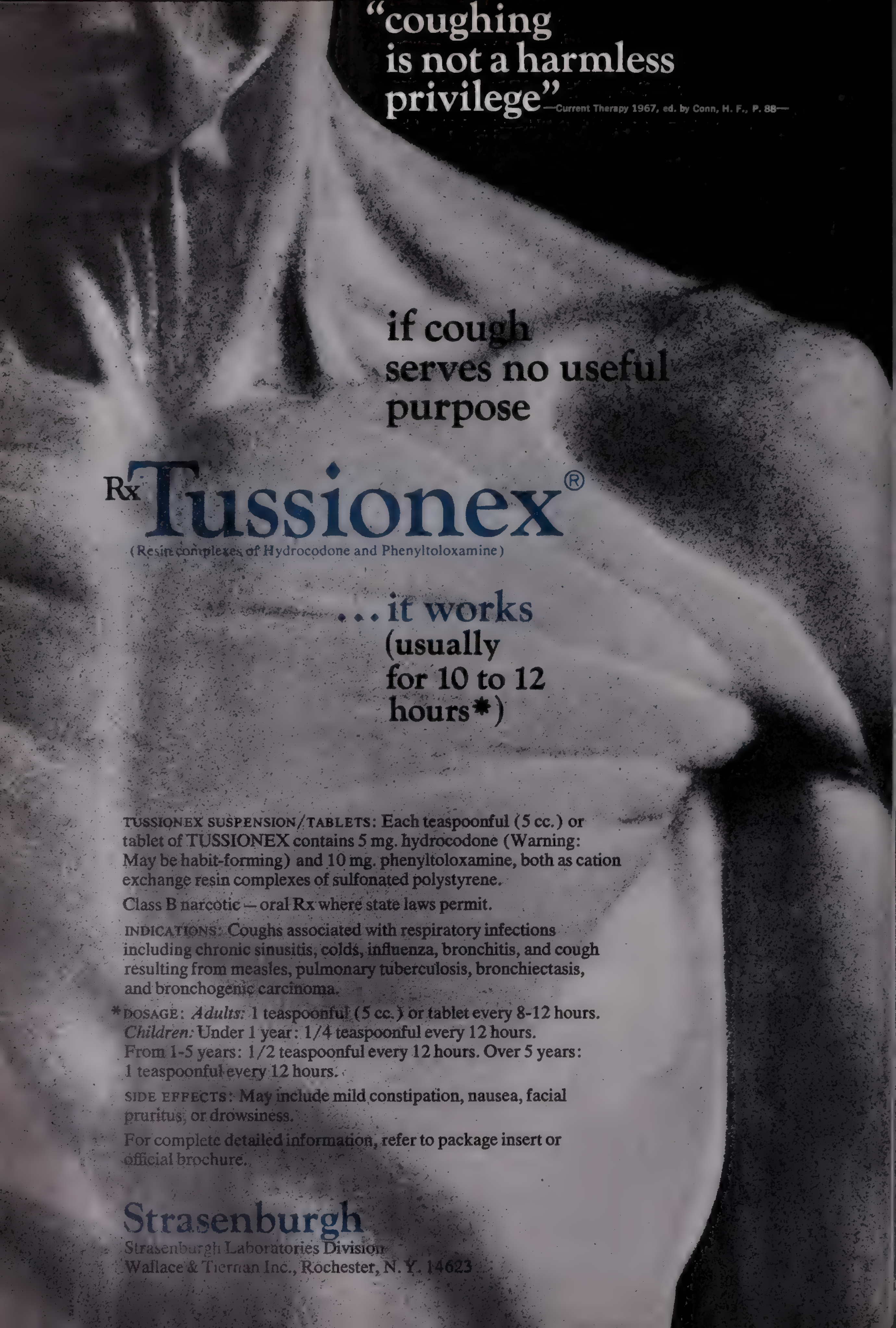

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Editorials

Management of Prostatic Infarcts

Elsewhere in this issue, Antolak* describes the successful management of a challenging patient with pyohydronephrosis secondary to prostatic infarction. The conservative approach to such a problem often results in a successful outcome, as dramatically outlined. Nephrostomy drainage in the face of a solitary kidney containing a calculus, with lower ureteral obstruction, was instrumental in achieving a rapid recovery. Roberts and Lattimer[1] have shown similar effective improvement in renal function by catheter drainage of prostatic obstruction as measured by 184% improvement in the creatinine clearance.

Also, in spite of a sterile urine culture, the utilization of antibiotics demonstrated judicious care, as the patient had previously received penicillin which may mask ongoing infection.

Improvement occurred with upper tract drainage, antibiotic therapy and time, and set the stage for treatment of the obstructive lesion.

The rather sudden onset of obstruction of the bladder outlet, and clinical findings suggest another fascinating, obscure condition—granulomatous prostatitis, which also presents in this manner. The necrotizing granulomata, as described by Kelalis, Harnson and Utz[2] may respond to bladder drainage and steroid therapy.

Enzymatic determinations as well as microscopic tissue verification may prove of value. In a series of 96 open prostatectomies for benign disease, Howard and Fraley[3] found elevation of the acid phosphatase in eight cases. All had microscopic infarction of the prostate.

The progression of infarct of the prostate to abscess formation can similarly lead to sudden obstruction of the ureters as well as the bladder outlet. Drainage by transurethral unroofing, or by spontaneous intravesicle rupture (autoprostatectomy) can be most dramatic.

Thus an aggressive, logical, staged approach (often the more conservative ultimately) may result in significant patient salvage—whether the correct diagnosis is made preoperatively or not.

C. Richard McKinley, M.D.
Minneapolis, Minnesota

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*See page 591.

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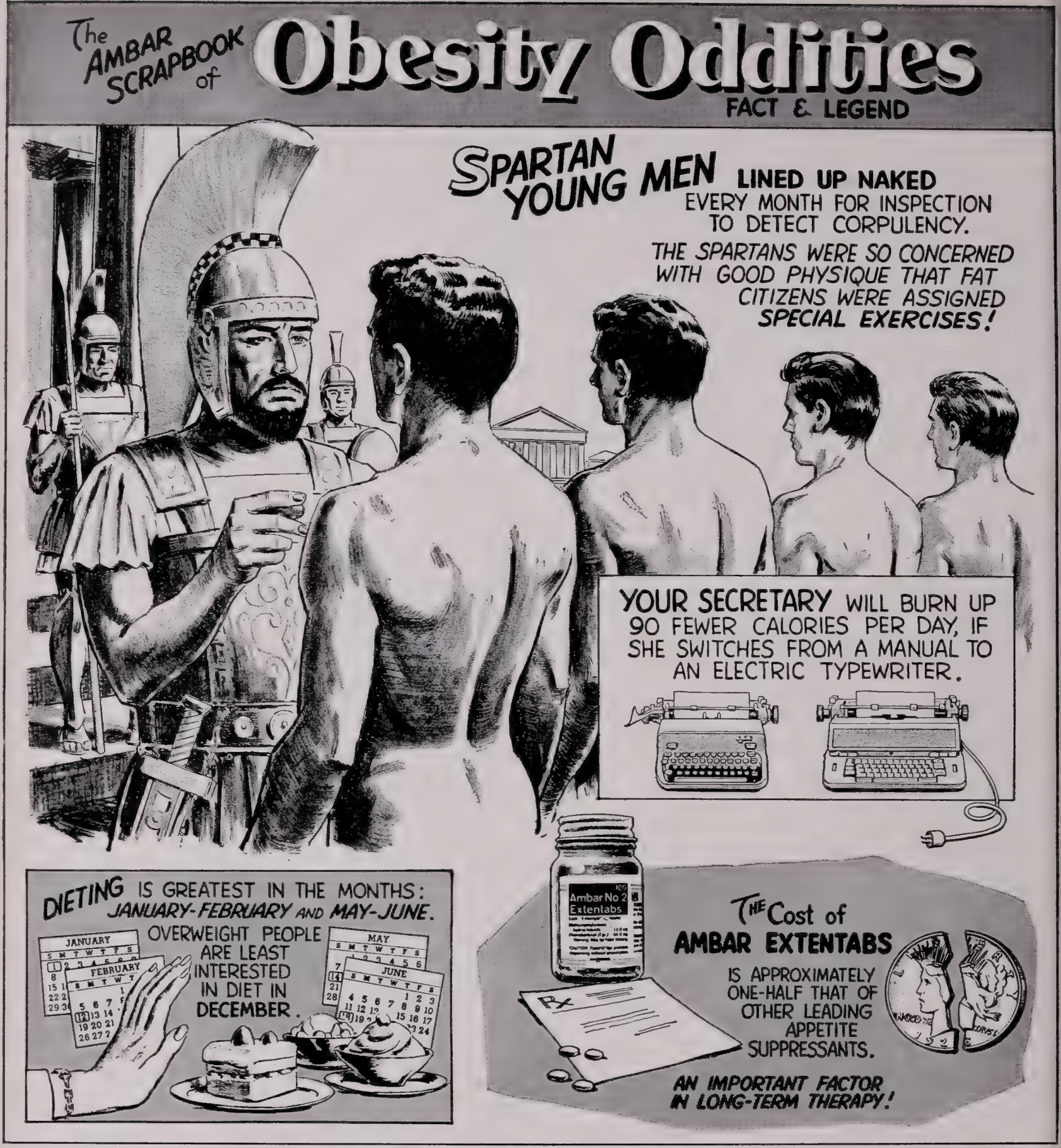
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BRIEF SUMMARY/**Indications:** Ambar suppresses appetite and helps offset emotional reactions to dieting. **Contraindications:** Hypersensitivity to barbiturates or sympathomimetics; patients with advanced renal or hepatic disease. **Precautions:** Administer with caution in the presence of cardiovascular disease or hypertension. **Side Effects:** Nervousness or excitement occasionally noted, but usually infrequent at recommended dosages. Slight drowsiness has been reported rarely. See package insert for further details.

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Intrasynovial Corticosteroid Therapy*

INTRA-ARTICULAR INJECTION of hydrocortisone or its derivatives is a valuable adjunct to treatment in many rheumatic diseases. Such injections are usually of temporary benefit, however, and must be coordinated with the overall plan of therapy for each patient. All diarthrodial joints (true joints) except the spinal joints may be injected. The advantage of intra-articular injection over systemic administration is that a high concentration of the hormone, with its anti-inflammatory effect, may be given to a desired local area while the total injected dose is relatively low. When the proper dosage is injected, usually only a small amount of the drug is absorbed into the systemic circulation, and the potential hazard of suppression of pituitary-adrenal function is thereby avoided. In addition to their use in rheumatoid arthritis, steroids injected intra-articularly are often effective in degenerative arthritis, acute gouty arthritis, traumatized joints and arthritis associated with psoriasis, ulcerative colitis, and systemic lupus erythematosus.

With injection of hydrocortisone acetate or other similar steroid derivatives, decrease in pain and swelling may occur in 90% of patients within 24 hours.[1] But improvement often lasts only a week or less. When the t-butyl acetate group is substituted for the acetate group of hydrocortisone or its derivatives, the steroid becomes less soluble and is more slowly hydrolyzed by body tissues. The action is thus prolonged to two weeks or longer. The work of Bilka and of others[2] suggests that the effect of triamcinolone hexacetonide is also prolonged.

Often intra-articular injections of corticoids are especially helpful when one or only a few joints are inflamed, painful, or particularly bothersome because of one of the conditions previously listed. Intra-articular injections of corticoids may be helpful when given with systemic treatment or when treatment with other medications is contraindicated. After an injection, the patient should be cautioned about over-using the injected joint, as the clinical improvement may encourage abuse of the joint, thus shortening the duration of effectiveness of the injection and causing irreversible damage to the joint. This is especially true of the weight-bearing joints.

Rheumatoid patients are not usually helped by intra-articular injections of corticoids when there is marked widespread activity or severe joint destruction and deformity. Intrasynovial injections of corticoids are contraindicated when a specific infection is responsible for the inflammation of the joint or when an infection is present in a periarticular region. Roentgenograms of the joint should be taken before injection. Culture of synovial fluid prior to injection should be considered when the diagnosis is uncertain or an atypical clinical picture is present.

Gene G. Hunder, M.D.
Rochester, Minnesota

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*Bilka, P. J.: A New Intra-articular Steroid with Prolonged Anti-inflammatory Action. Minnesota Med. 50:483, 1967.

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April 1 is the day upon which we are reminded of what we are on the other 364 days.—Mark Twain

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Some people are so sensitive that they feel snubbed if an epidemic overlooks them.—Frank Hubbard

Photo professionally posed.

No injection after all!

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Warnings: Acute anaphylaxis (may prove fatal unless promptly controlled) is rare but more frequent in patients with previous penicillin sensitivity, bronchial asthma or other allergies. Resuscitative (epinephrine, aminophylline, pressor amines) and supportive (antihistamines, methylprednisolone sodium succinate) drugs should be readily available. Other rare hypersensitivity reactions include nephropathy, hemolytic anemia, leucopenia and thrombocytopenia. In suspected hypersensitivity, evaluation of renal and hematopoietic systems is recommended.
Precautions: In suspected staphylococcal infections, perform proper laboratory studies including sensitivity tests. If overgrowth of nonsusceptible organisms occurs (constant observation is essential), discontinue penicillin and take appropriate measures. Whenever allergic reactions occur, withdraw penicillin unless condition being treated is considered life threatening and amenable only to penicillin. Penicillin may delay or prevent appearance of primary syphilitic lesions. Gonorrhea patients suspected of concurrent syphilis should be tested serologically for at least 3 months. When lesions of primary syphilis are suspected, dark-field examination should precede use of penicillin. Treat beta-hemolytic streptococcal infections with full therapeutic dosage for at least 10 days to prevent rheumatic fever or glomerulonephritis. In staphylococcal infections, perform surgery as indicated.
Adverse Reactions: (Penicillin has significant index of sensitization): Skin rashes, ranging from maculopapular eruptions to exfoliative dermatitis; urticaria; serum sickness-like reactions, including chills, fever, edema, arthralgia and prostration. Severe and often fatal anaphylaxis has been reported (see "Warnings").
Composition: Tablets—125 mg. (200,000 units), 250 mg. (400,000 units), 500 mg. (800,000 units); Liquid—125 mg. (200,000 units) and 250 mg. (400,000 units) per 5 cc.

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Tremetol Intoxication (Milk Sickness)*

The author is to be commended on a comprehensive description of a perplexing, frequently lethal, formerly common, but fortunately rare poisoning at the present time.

Tremetol intoxication may pose a challenging diagnostic problem to the physician who is confronted with a patient suffering from it, and it may be confused with severe diabetic acidosis or salicylate intoxication. These were the initial diagnostic impressions in the patients reported by Dr. Hartmann, Sr., et al., but a normal blood sugar and the absence of sugar in the urine precluded diabetes mellitus, and a normal or low serum salicylate quickly ruled out salicylate intoxication.

Characteristically, the acidosis (ketosis) of tremetol intoxication is resistant to fluid and alkali therapy, as exemplified by the cases reported by Dr. Hartmann, Sr. et al. The first case, a twelve-year-old girl seen in 1946, with an initial serum CO_2 content of 4 mEq/L, required 11.5 mM/kg. of sodium lactate, 32 mM/kg. of glucose, and 8 mM/kg. of hypotonic Ringer's solution administered over a 48-hour period in order to correct the acidosis. Most other types of acidosis respond to treatment in 12-24 hours. The second patient, a seven-month-old girl, was admitted in December 1962, with an initial serum CO_2 content of 4.8 mEq/L. She required 25 mM/kg. of sodium lactate, 10 mM/kg. of sodium bicarbonate, 90.5 mM/kg. of glucose, and 10 mM/kg. of hypotonic Ringer's administered over an 85-hour period to correct the acidosis. This is the most refractory case of acidosis in our records. The third case, a twenty-month-old girl (sister of Case 2), was admitted five days after her sister's discharge with an initial serum CO_2 content of 9 mEq/L. She responded to treatment in 24 hours with 17.5 mM/kg. of sodium lactate, 13 mM/kg. of glucose, and 6.25 mM/kg. of hypotonic Ringer's. The acidosis in this girl was due entirely to ketosis. Her serum ketone level was 15 mEq/L.

Unfortunately, tremetol poisoning may last a long time and may produce repeated bouts of acidosis, precipitated especially by infections in children. This happens even though the contaminated milk is removed from the diet. The twenty-month-old girl (Case 3 above) was readmitted two months after her first admittance with severe acidosis precipitated by measles (rubeola). Her seven-month-old sister (Case 2 above) was readmitted one year and eight months after her first admittance with severe acidosis precipitated by a respiratory tract infection. Both girls continued to develop ketosis with each respiratory infection up to the present time, four years after their first admittances.

The excellent work of Dr. Anna Pierce Bixby shows what an astute clinician on the battlefront of disease can accomplish without a great deal of laboratory assistance.

A. F. Hartmann, Jr., M.D.
St. Louis, Missouri

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*Snively, W. D., Jr.: Mystery of the Milksick. Minnesota Med. 50:469, 1967.

Adolescence*

The actions and problems of youth seem to be an eternal and persistent concern of those who are no longer young, and particularly so if one lives under the same roof with one or several adolescents. Problems among the young today may be either greater or only more widely publicized, and youth may, in effect, be libeled on the front pages of newspapers for every spectacular affront to our mores. These affronts may be all the greater because they often touch too transparently on the hypocrisies of those of us who have "settled down." Our outrage and our tendency to categorize acts in terms of crime and punish-

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*Schechter, M. D.: A Psychological Field Theory of Adolescence. Minnesota Med. 51:1841, 1968.

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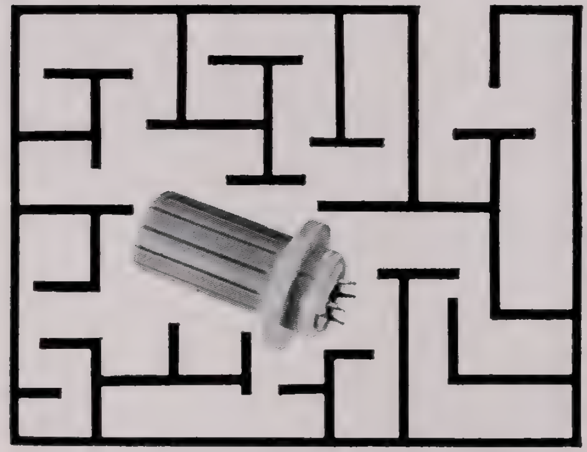

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ment or of law and order make us overlook the need for justice and compassion.

Physicians, in particular, need to be aware that beneath those activities and mannerisms that seem obnoxious, there may frequently be issues that are not just matters of conflict between generations but represent the extremes of those persistent problems that all young people share in growing up. A central source of these problems is discussed at length in a scientific article found elsewhere in *Minnesota Medicine,* which speaks clearly to a central problem of a significant number of adolescents: a problem that may be obscured by the superficial manifestations or assertions of a particular youth. The medical issue that may be encountered most frequently, however hidden, is that of a depressive reaction, which may involve all the unique anguish of a given individual but may be masked by his automatic social efforts to overcome, deny, obscure his personal suffering.

The physician will usually be called upon by the parents, and their concerns may be couched in terms of the "incomprehensible" behavior of their sons or daughters. If the physician is aware of other possibilities, and if he can take a wise rather than an authoritarian stance and look beneath social manifestations, he will often find an adolescent in need of help and willing to receive it if it can be presented with dignity and compassion and without adverse or punitive responses.

Each problem will naturally have an individual stamp despite social or clinical similarities; hence one will have to seek individual approaches to treatment. Despite these variations, however, most of the difficulties will probably involve the basic issue leading to the common problem of depressive reaction: namely, the process of gradual emotional separation from one's parents in an automatic way. Many of the superficial, social trappings are only a part, and often an insignificant one, of the individual effort to assert that separation and independence and to deny that it is hurtful and difficult. If the physician can be aware of this and recognize it, he will be able to help with the problems that lie beneath the surface.

James G. Delano, M.D.
Rochester, Minnesota

Mitral Valve Reconstruction

ONE OF THE MOST dramatic recent developments in the field of cardiac surgery has been the perfection of satisfactory prosthetic devices for total replacement of irreparably damaged cardiac valves. Many thousands of patients are now enjoying good health because of these advances. Nevertheless, it is always preferable to preserve the patient's own valve with reconstructive techniques, whenever this is possible. The long-term complications of the use of prosthetic valves, particularly that of thromboembolism, preclude unwarranted replacement of any damaged valve if reconstructive methods can provide good functional results. This philosophy has been emphasized recently by Drs. Kiser, Peterson, and Johnson in the July 1968 issue of MINNESOTA MEDICINE.*

In most cases, mitral stenosis without calcification and without appreciable mitral insufficiency can be very satisfactorily repaired, and rarely is mitral valve replacement indicated. There is no unanimity of opinion on whether the closed (non-bypass) or open technique should be used for the repair of mitral stenosis. With the perfection of safe methods of cardiopulmonary bypass, mitral stenosis is being repaired under direct vision by increasing numbers of surgeons. The open approach permits a more consistent division of both commissures and greater relief of subvalvular stenosis than closed techniques provide. Mitral regurgitation may be corrected when it is found or produced (as in Case 3 of Kiser and Johnson), and thrombi in the atrium may be completely and safely removed when they are unexpectedly encountered. The left atrial ap-

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*Kiser, J. D., Peterson, T. A., and Johnson, F. E.: Mitral Valve Reconstruction. Minnesota Med. 51:897, 1968.

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pendage can be closed if desired to prevent further thrombus formation at that site.

The *open approach to the valve* is preferable in patients with combined mitral stenosis and insufficiency, because there is no satisfactory way to treat valve insufficiency by a closed procedure. Likewise, patients with calcification of the valves, previous embolism (the incidence of intracardiac thrombosis may be as high as 37% versus 19% in patients without embolism),[1] and clot in the left atrial appendage deserve the benefits of open surgery to decrease the incidence of embolic complications. Perhaps long-standing atrial fibrillation should also be included as an indication for open operation because of the much greater incidence of associated left atrial thrombi.[1]

The *mortality rate* for open operation on pure mitral stenosis with a pliable valve can be less than 2%[2,3] and is comparable to that for closed commissurotomy. Many surgeons have adopted open techniques for all patients with mitral stenosis and believe that their results have been improved by this change.[2,4,5] There is also the theoretical advantage that if the valve is opened completely and all insufficiency is repaired, the onset of re-stenosis and the need for re-operation may be either delayed or eliminated. While it is generally agreed that open surgery is indicated in complicated cases of mitral stenosis, its place as a routine procedure in all cases cannot be definitely defined until long-term results are evaluated.

Mitral insufficiency may result from malfunction of any of the four parts of the valve —the mitral annulus, the valve leaflets, the chordae tendineae, and the papillary muscles. Because the clinical picture of mitral regurgitation may result from a diversity of pathologic changes and since no single method of correction can be applied in all cases, open cardiac repair is necessary for uniform assessment of the pathologic anatomy of the diseased valve and application of the proper corrective operation.

Clefts, tears, or perforations of the leaflet may be seen in congenital cleft mitral valves, in traumatic insufficiency produced during the correction of mitral stenosis, and following cure of subacute bacterial endocarditis. These circumstances represent favorable lesions for treatment; and direct suture or patching of the defect, with or without concomitant annuloplasty,* has usually given an excellent result.

Insufficiency resulting from *rupture of chordae tendineae* may be corrected by a number of techniques. Successes have been obtained with the use of artificial chordae and with re-suture of the chordae (or free edge of the leaflet) to the normal point of attachment. We prefer plication of the valve in the area of absent chordae combined with a posterior annuloplasty.[6,7] Because the other portions of the valve are essentially normal, results of repair have usually been excellent.[7] Even though isolated patients may later develop evidence of recurrent mitral insufficiency, repair is generally preferable to replacement of the valve, particularly in younger patients.

In some cases, mitral insufficiency is caused by dilatation of the entire valve ring, and the valve tissue itself is only minimally deformed. Annuloplasty, a selective shortening of the mitral annulus, narrows the valve orifice and allows the valve leaflets to approximate. When applicable, this technique yields very satisfactory results and avoids the complications associated with valve replacement.

The main *disadvantage of annuloplasty* is the problem of late recurrence of mitral insufficiency—a difficulty which has led to the abandonment of the technique by some surgeons. The incidence of recurrence may be decreased by "overcorrection" and by proper placement of deep, strong sutures, preferably backed up with fabric pledgets to help prevent them from pulling through the myocardial tissues. The procedure is most successful in young patients with good tissues and in hearts of moderate size. In some instances, the basic pathologic process of annular dilatation continues and insufficiency recurs. This is more likely to happen with myocardiopathies, Marfan's syndrome, and coronary artery disease—conditions in which valve replacement may be preferable.

Valves that have lost significant leaflet substance and those that are damaged by extensive fibrosis and calcification cannot be restored to satisfactory function by valvuloplasty techniques; such valves must be excised and replaced with a prosthesis. Similarly, lesions of mixed mitral stenosis and insufficiency usually

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*See Test Your Word Score Page 672.

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require prosthetic replacement for best results.

Tricuspid insufficiency is frequently associated with mitral valve disease. It may be "functional" because of dilatation of the annulus secondary to an enlarged right ventricle, or it may develop from organic changes in the valve leaflets caused by rheumatic scarring. The leaflets are relatively normal in functional tricuspid insufficiency, although they exhibit some thickening and other minor abnormalities. Organic tricuspid insufficiency may be suspected if the right ventricular pressures are normal; but it is virtually impossible to differentiate organic from functional insufficiency by palpation alone, unless there is associated valvular stenosis. Because of the difficulty of assessing the tricuspid valve preoperatively, it is routinely palpated in every case of open mitral valve surgery.

Surgical correction of functional tricuspid insufficiency by methods other than valve replacement has met with varying success. In general, techniques of mitral annuloplasty cannot be transferred directly to the tricuspid valve, and attempts to do so have usually given poor results. We have had the greatest success with a type of annuloplasty which obliterates the posterior cusp, converting the valve into a bicuspid one. The heart is allowed to beat, the right ventricle is then filled with blood, and competency of the valve can then be inspected under direct vision. With few exceptions, functional tricuspid insufficiency can be completely corrected by this technique, and valve replacement may be avoided. It adds less than 10 minutes of bypass time, and the long-term results have been excellent.

A satisfactory tricuspid annuloplasty offers an alternative to valve replacement or a "do-nothing" approach.[8,9] We feel it is important to perform an annuloplasty in all cases where the insufficiency is of more than mild severity, even if it is deemed functional and reversible. Postoperative cardiac output is improved, and perhaps there are a few more survivors among patients who would otherwise die of "low-output syndrome." In addition, convalescence is speeded and fluid-retention problems are minimized. Finally, one avoids the situation of the occasional patient who has a disappointingly poor result from his mitral valve surgery because of failure of the tricuspid insufficiency to regress spontaneously.

The authors include two cases in which it was necessary to replace the aortic valve with a prosthesis. Our experience[10] and that of others[11] would indicate that the incidence of postoperative embolization is no greater for multiple valve replacement than for single valve replacement. Consequently it is less imperative that all attempts be made to preserve the mitral valve if other valves require replacement with prostheses. Certainly if there is any question about the functional result following valvuloplasty, replacement should be undertaken.

In addition to avoiding the postoperative complications of prosthetic valves, mitral valve repair by reconstructive techniques is accompanied by a lower operative mortality than valve replacement. The mortality for mitral annuloplasty in suitable cases is approximately half of that for valve replacement, and open mitral commissurotomy can be performed with only a fraction of the mortality of valve replacement. We therefore concur that the preservation of the patient's own tissues, if repair can be accomplished without compromise of the functional result, is far preferable to a replacement with any mechanical prosthesis now available.

Gordon K. Danielson, M.D.
Rochester, Minnesota

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6-11. May be secured from the author or the reprints.

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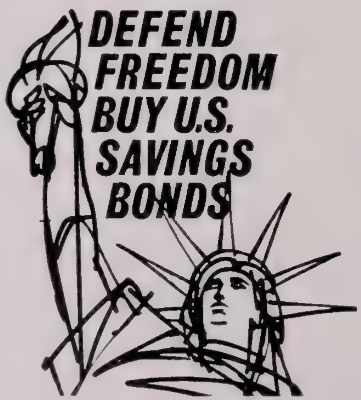
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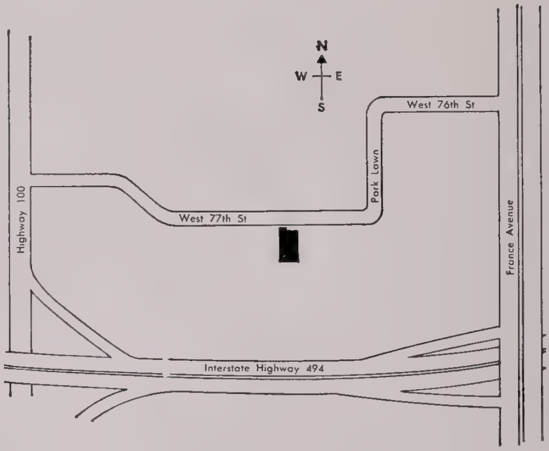
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The Editor's Soliloquy

Medical Education

THE SURVEY of Doctors I. J. Fahs and W. R. Miller* was gratifying to read, confirming the suspicion that a large percentage of doctors devote considerable time to keeping up with the advances of medicine by reading well-written current medical journals, books and other medical literature.

Classifying 13 sources of medical information they state that specialty societies, postgraduate courses, medical journals and medical books predominate in providing opportunity for advance and progressive medical education. County and national medical society meetings and the costly ($14,000) Minnesota television "Monday for Medicine" series rank very low, along with the teaching tapes and the courteous, gracious and welcome calls of the patient detail men, as the least valuable source of medical information.

According to Doctors Fahs and Miller's Survey, "Each physician works out his own unique way of striving to keep abreast of expanding medical information. He may thoroughly digest the contents of one medical journal to the exclusion of all others, he may concentrate on attending scientific lectures by selected experts, he may ingeniously 'pick his colleagues' brains' in informal contact, or he may utilize all of these and other methods to varying degrees."

Although the specialty medical societies are considered high on the list of those providing worthwhile continuing medical education, considerably above the state and national medical meetings, these latter organizations are most valuable in allowing doctors to renew their social acquaintances and thereby establish intimate and harmonious rapport. To be sure there is a very considerable amount of up-to-date medical knowledge available in the state and national meetings, but the majority of doctors do not consider this source to be as valuable as current medical literature which can be assimilated at their own private moments of relaxation.

Having an eye for economy and endeavoring to obtain the greatest value at the least expense, similar to what the Medical Association recommended to the Federal Government pertaining to Medicare, it is probable that this Association will discontinue the expensive Monday night television series, which ranks lowest in importance as a source of medical information for doctors.

Carl O. Rice, M.D.

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*Patterns of Continued Medical Education, Northland News, Vol. II, January 1969. Dr. Winston Miller is Director of the Northlands Regional Medical Program.

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Stanley R. Maxeiner, M.D.

The Editors are pleased to publish the address given by Mr. George D. McConnell on the occasion of the presentation of the St. Barnabas Bowl Award to Dr. Stanley R. Maxeiner, Sr., January 15, 1969.

I AM SURE that most of you are familiar with the St. Barnabas Bowl Award. It was inspired by and made possible through the generosity of Mr. Charles Bolles Rogers, who was the President of the Board of Trustees of St. Barnabas Hospital from 1946 to 1951. It was designated to be given to the physician who, in the opinion of the members of the Hennepin County Medical Society, by reason of his professional contribution on the basis of medical research, achievement or leadership, has become the outstanding physician of this and other years. This award has been given since 1952, with the exception of three years when no selections were made. Of the 14 recipients of this award, eight are still living and four of these eight are with us tonight.

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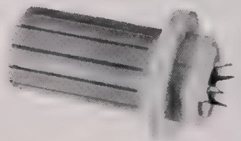

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Tonight's recipient of the 1969 St. Barnabas Bowl Award, Dr. Stanley R. Maxeiner, has served his profession through six decades. As he has won many previous honors, winning still another award is not new to him.

Dr. Maxeiner was born in Chippewa Falls, Wisconsin, in 1885 and grew up there. His first exposure to surgery came in a most personal way. When he was in high school he was detailed to hold a leg for an amputation while the local doctor cut it off. I suppose this had a great deal to do with the fact that Dr. Maxeiner later selected surgery as his life work.

In 1909 he achieved the M.D. degree from the University of Minnesota and entered internship at the Minneapolis General Hospital. This was the beginning of a long association with Dr. Robert Emmett Farr, the surgeon under whose preceptorship Dr. Maxeiner learned and contributed to the young specialty of surgery. General anesthesia in those days was an inexact and dangerous business. Dr. Farr had pioneered in the development of techniques of local and regional anesthesia; Dr. Maxeiner underlaid these techniques with research reported in Dr. Farr's classical textbook. His mastery of local anesthesia, and of the gentle surgical touch which must go with it, pervaded all his teaching to subsequent surgical generations.

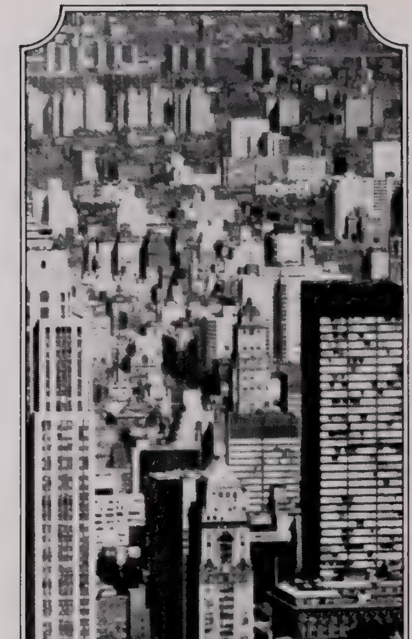
Dr. Maxeiner served as attending surgeon at the Minneapolis General Hospital. At the founding of the U. S. Veterans' Hospital in Minneapolis, he became attending surgeon and surgical consultant, where he worked and taught for over 35 years. He loved to teach as well as to work. He contributed extensively to surgical literature. His academic appointments to the Department of Surgery at the University of Minnesota reached the rank of Clinical Professor in 1949, from which he has now retired.

In 1917 and 1918 he served as a Captain in the Medical Corps. He was sent at once to France where he served in British trenches for 16 months and where he sustained a permanent hearing loss from shell-fire.

After resuming his practice, he became aware that he and his colleagues had common problems and common needs and that some kind of a forum or meeting ground was required to solve these needs. In 1922 he met with three other surgeons, Drs. Webb, Zierold and Dunn, and formed the Minneapolis Surgical Society. During the same year he contributed to the formation of the Minneapolis Clinical Club, which was designed to bring men of different specialties together for fellowship and for cross-pollination. This society became the Minneapolis Academy of Medicine. He served as president in the early years of both of these societies. He also became a member of the Minnesota Academy of Medicine, the Western Surgical Society, the American College of Surgeons, and the Founders Group of the American Board of Surgery. He has served both the Hennepin County Medical Society and the Minnesota State Medical Association as a member and as president. Privately he has served innumerable colleagues over the years as consultant, adviser, and friend. He can look back over the years and see the development of surgery into a science, a discipline, and a compartment of medicine.

Dr. Maxeiner is now retired. He shares his days now with his companion of 47 years, his wife Madeline. They like to travel, they like to grow roses, and he plays golf—the third love of his life.

His special joys, however, are the opportunities which he has to see his son, Dr. S. R. Maxeiner, Jr., working in the same vineyard, seeing patients whose lives are better for what he has done for them, and seeing surgeons



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who once listened to his teaching and are now making their own contributions to medicine and the community.

Dr. Maxeiner, your great passion for medicine and your compassion for your associates and your patients have earned you this award.

George D. McConnell
Board of Directors, St. Barnabas Hospital

Chairman's Letter

(Continued from page 571).

Brunn has been of tremendous help to the Committee in investigations and recommendations. The doctors previously given a grant are visited twice a year or oftener by a committee member and current reports are made at each meeting. Presently receiving grants are seven widows and no physicians.

Through the years the physician-in-need has been a fascinating subject to contemplate. These men are frugal, not demanding, grateful and fiercely proud and independent. They accept help from their colleagues but would starve before asking for government aid. Their honesty and integrity is demonstrated time and again. A recipient receiving $75.00 monthly wrote to tell us that he had finally outlived an insurance policy, that the insurance company would now send him $25.00 a month for life, and would we please reduce his draw to $50.00. A couple on a fund grant received a small bequest unknown to the Committee and returned our monthly check stating that they would let us know when the $5,000.00 was gone and when we should resume payments.

In a number of instances a widow of a physician has changed her will to leave properties to the Committee. No such bequests have been realized as yet.

If you know of a destitute physician or a widow of a physician in genuine need, call your county medical society secretary, Mr. Harold Brunn or me. We stand ever ready to don our shining armor, mount our milk-white steeds and gallop off to relieve distress and oppose the forces of evil, all with your money.

The Committee has an unparalleled and unmatched record for attendance at meetings. The diligence and devotion of these men make chairing this group my most enjoyable duty for the State Association. At the call of the Chairman they come from the far corners of the state in the foulest weather and despite impossible driving conditions. With the notable exception of the chairman, none of them are young.

Of the original eighteen-man committee under Dr. Humphrey, three are still serving; Dr. Paul Boman of Duluth, Dr. Herman Juergens of Belle Plaine, and the present chairman, Dr. James A. Blake of Hopkins. Meetings of the group are attended by fourteen or fifteen of the eighteen at all times, with occasional one hundred per cent turnouts.

James A. Blake, M.D., Chairman,
Committee on Physicians' Assistance

Nature is the most thrifty thing in the world; she never wastes anything; she undergoes change, but there's no annihilation; the essence remains—matter is eternal.—Binney

A saint is a dead sinner revised and edited.—Ambrose Bierce

What's Your Score in Alcohol?

Problem: A city street after midnight; a car and its driver; suddenly, a pedestrian off the curb and in the road; no time to avoid him; the walker is struck and killed. A common story. Chances are the pedestrian was "under the influence." True or False?

Answer: True. Studies show that 40% of pedestrian fatalities died with blood levels of 100 mg% of alcohol or more, a level which always impairs cerebral functions.

Problem: The police officer who interrogated the driver at the accident scene found him to be middle-aged, well dressed, employed, driving a late-model car, and residing in a comfortable home nearby. This driver, as a responsible citizen, can surely be assumed to have no drinking problem. True or False?

Answer: False. Only one alcoholic in ten is in skid row. Nine problem drinkers out of ten keep their places in society.

Problem: The police officer detected some odor of alcohol. However, the driver could stand steady and walk straight. The police officer could be sure the driver was not "under the influence." True or False?

Answer: False. He couldn't be sure, and neither could you. Tests show blood levels of 100 mg% commonly go unrecognized even by physicians. Degrees of intoxication obvious in a complex activity like driving may be inapparent in the simple tests usually performed for sobriety. The only meaningful test of intoxication is actual measurement of alcohol levels in blood, breath, or urine.

Problem: Despite obstacles, the police officer was able to secure a legal and valid determination of blood alcohol. The measured concentration was 120 mg%. State law defines 100 mg% or more as intoxication. The driver just had the bad luck to get caught. It takes only a few drinks or so to raise blood alcohol to this level. It could happen to anybody. True or False?

Answer: False. 120 mg% is not attained by ordinary drinking; it follows sustained, heavy intake. Blood alcohol concentration depends upon body weight, metabolic state, and span of time, as well as intake. It is therefore difficult to say how much drinking 120 mg% of blood alcohol may represent. One can estimate that a 150-pound man would require 8 ounces of hard liquor within an hour, or one highball every 10 minutes, steadily, one after the other. This amount of drinking doesn't "just happen" to anybody; it indicates a problem drinker.

Problem: It is not important for society to identify the problem drinker, for he (or she) knows his own problem and can seek help. True or False?

Answer: False. Typically the problem drinker is the last to know. Alcoholism becomes a disease when the patient can no longer control his drinking. He has slid into his affliction insidiously and has built up his deceptions step by step. He may not recognize them himself.

Problem: Recognition is still not important, for treatment doesn't make much difference anyway. True or False?

Answer: False. Alcoholism is a chronic disease with a high incidence of reactivation. It is difficult to treat *but not hopeless.* Non-medical therapists including alcoholics themselves have succeeded in thousands of cases. Unfortunately, interested physicians have been few. Medical research has concerned itself with the complications of alcoholism rather than the disease itself. Perhaps the trouble with treatment lies less in the disease and more in medical reluctance. Medicine must become willing to establish an early diagnosis, to be scientific and definitive in testing and therapy, and to join with other workers in this broad social problem.

Continued to page 622.

Curbstone Consultation

Osteomyelitis

QUESTION: A 13-year-old girl sustained a relatively minor fracture of the posterior of the tibia and a short leg cast was applied. Three weeks later the leg was considerably swollen and six weeks later an obvious osteomyelitis was evident. Antibiotics were then given and the systemic symptoms subsided, but a sinus tract developed in the leg. Could this have been prevented?

ANSWER: Timing of antibiotic therapy is most important in the control of this condition. The antibiotic therapy may be effective in overcoming the systemic manifestations, but ineffective in overcoming the local lesion. Insofar as the lesion is concerned, the antibiotics must be administered in plentiful amounts before the lesion walls off. Otherwise, the antibiotics become ineffective. In this case, even with antibiotic therapy, the systemic manifestations subsided while the local symptoms increased. Early decompression of the involved area could probably have prevented the ischemic necrosis. There is still some disagreement as to the best time for surgical intervention. The timing is often quite difficult. After a few days, if the local symptoms do not subside, the area should be opened. A simple incision through the skin and several large drill holes or a window through the bone, is usually all that is necessary. The area is flushed with antibiotic solution, the window is closed, and antibiotic therapy is continued.

Vitamin B_{12}

QUESTION: Is vitamin B_{12} of value in the treatment of diabetic retinopathy?

ANSWER: There is no substantial evidence of vitamin B_{12} deficiency in diabetics or that such a deficiency plays a role in the etiology of diabetic retinopathy. Therefore, therapy with vitamin B_{12} would not seem to be indicated in the treatment of that condition.

Beware lest you lose the substance by grasping at the shadow.—Aesop

What's Your Score in Alcohol?

(Continued from page 620)

Problem: These criticisms of the medical community may not apply to you. For example:

a. You are alert to the early symptoms and signs of loss of control in alcoholism.

b. You can determine, in your regular medical laboratory, the concentration of blood alcohol in any patient at any time, just as you would determine the concentration of blood sugar.

c. You know where to secure for any alcoholic patient a balanced, long-term therapeutic effort by a treatment team in which a physician plays an appropriate, knowledgeable, and responsible part. True or False?

S. R. Maxeiner, Jr., M.D.*
Minneapolis, Minnesota

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*Chairman, Committee on Automotive Injuries, Minnesota State Medical Association and Chairman, Minnesota Committee on Trauma, American College of Surgeons.

Reference

Support for the facts and opinions in these statements may be found in "Alcohol and Highway Safety", a report from the Secretary of Transportation to the Congress of the United States, submitted August 2, 1968. (Superintendent of Documents, Washington, D. C., $.50)

All the King's Horses

Otto von Guericke, in studying air and its effects, created what is said to have been the first man-made vacuum. He made two halves of a heavy metal sphere, the parts that met having been machined so accurately that when put together they were air-tight. He also invented a stopcock through which he pumped out the air.

"Not all the king's horses can pull them apart," he said.

"They can't, eh?" said the King of Prussia. "Prove it."

So von Guericke attached strong handles to the hemispheres. Ten of the king's horses were hitched to each hemisphere. For an hour they pulled steadily and even jerked. The hemispheres could not be pulled apart. When all present admitted that even the twenty king's horses could not unlock the two parts, von Guericke turned the stopcock with one finger and let in the air. Instantly the two parts fell apart.*

---

*Pegmatites.

Prescription for Youth

1. Avoid fried meats which angry up the blood.
2. If your stomach disputes you, lie down and pacify it with cool thoughts.
3. Keep the juices flowing by jangling around gently as you move.
4. Go very light on the vices, such as carrying on in society—the social ramble ain't restful.
5. Avoid running at all times.
6. Don't look back—something might be gaining on you.

Satchell Paige

The true value of a human being is determined primarily by the measure and the sense in which he has attained liberation from the self.—Albert Einstein

The Viewing Box

A Moveable Abdominal Mass

The x-ray films below are from the colon (Figure 1) and the small bowel (Figure 2) studies performed on a 49-year-old white female whose chief complaint was an enlarging abdomen. Physical examination showed a large firm mass in the left mid-abdomen which the patient stated had enlarged over the past six months. It was moveable laterally but not up or down. No other signs or symptoms were present.

The barium-filled small bowel film shows medial and posterior (corroborated by lateral films) displacement of bowel loops around a well-defined lucent area in the abdomen. (On this film, some barium remains in the colon from the preceding colon study.)

What is your diagnosis? (See next page.)

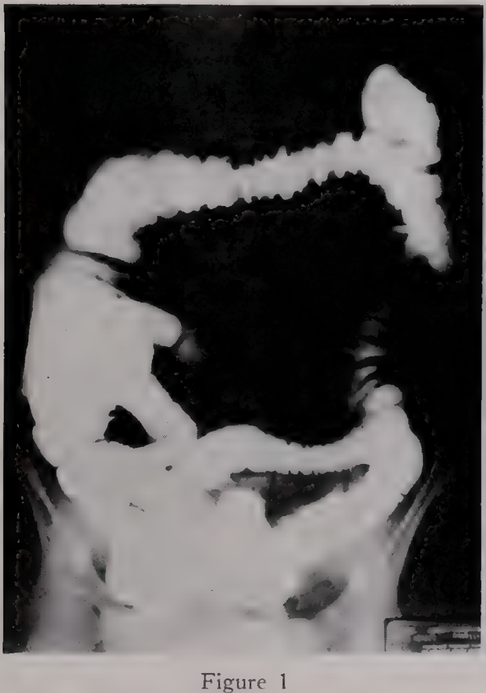

Figure 1

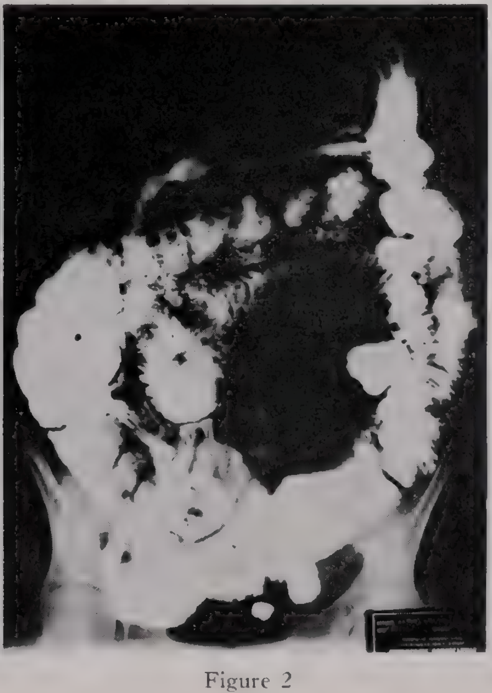

Figure 2

Diagnosis: Mesenteric cyst.

Following the x-ray studies, surgery was performed and a well-encapsulated cystic mass was encountered at the root of the mesentery. The mass was shelled out in toto; pathologically it was a pseudocyst containing a rather thick lymphoid material.

Discussion

Cysts of the mesentery are rare lesions. They give rise to varied and noncharacteristic symptoms. On physical examination, a moveable abdominal mass is palpated. Roentgen signs are fairly characteristic on barium examination of the small bowel. Plain film study usually shows an ill-defined soft tissue radiodensity. On barium contrast studies of the small bowel, the mass is sharply delineated as it is surrounded by loops of bowel (Figure 2). Its position and roentgen appearance place it in the mesentery, and this helps to rule out other possible abdominal masses. Unless very large, no obstructive signs are present. The bowel is displaced but not invaded or compressed. Occasionally the cyst wall will be calcified. Treatment is surgical removal with or without sacrificing a segment of the small bowel, depending on the cyst's location in the mesentery and its relationship to the small bowel loops themselves.

Robert D. Bugby, M.D.*
Minneapolis, Minnesota

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*Radiologic Consultants

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School of Salernum

They that in Physick will prescribe you food,
Six things must note we heere in order touch,
First *what it is,* and then *for what 'tis good,*
And *when* and *where, how often,* and *how much:*
Who note not this, it cannot be withstood,
They hurt, not heale, yet are too many such.*

Editor's note: It cannot be denied that in their capacity as advisers about nutrition too many doctors are deficient when they fail to inform their patients on what, why, when, where, how often, and how much to eat. The school knew the value of remaining in physical trim.

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*Regimen Sanitatis Salerni

Ugliness

It was not until I had attended a few post-mortems that I realized that even the ugliest human exteriors may contain the most beautiful viscera, and was able to console myself for the facial drabness of my neighbors in omnibuses by dissecting them in my imagination.—J. B. S. Haldane

Virtue

Be not simply good; be good for something.—Thoreau

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a vial:
the spasm
reactors
in your practice
deserve

Main S
DONNATA
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3 time

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	each tablet, capsule or 5 cc. of elixir (23% alcohol)	each Donnatal No. 2	each Extentab®
hyoscyamine sulfate	0.1037 mg.	0.1037 mg.	0.3111 mg.
atropine sulfate	0.0194 mg.	0.0194 mg.	0.0582 mg.
hyoscine hydrobromide	0.0065 mg.	0.0065 mg.	0.0195 mg.
phenobarbital	(¼ gr.) 16.2 mg.	(½ gr.) 32.4 mg.	(¾ gr.) 48.6 mg.
(Warning: may be habit forming)			

Brief Summary. Blurring of vision, dry mouth, difficult urination, and flushing or dryness of the skin may occur on higher dosage levels, rarely on usual dosage. Administer with caution to patients with incipient glaucoma or urinary bladder neck obstruction. Contraindicated in acute glaucoma, advanced renal or hepatic disease or a hypersensitivity to any of the ingredients.

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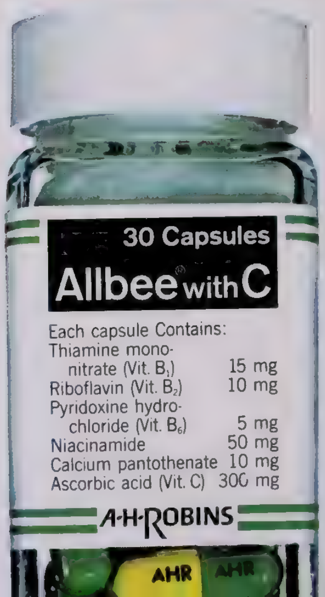
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Each capsule Contains:
Thiamine mononitrate (Vit. B1) 15 mg
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Niacinamide 50 mg
Calcium pantothenate 10 mg
Ascorbic acid (Vit. C) 300 mg
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Fracture-Trauma Conference

Nerve Injuries in Fractures of the Lower Extremity

Dr. Einer W. Johnson:*

The incidence of sciatic nerve palsy in dislocation of the hip is probably about 16%, the exact number depending on whose report you read. The incidence of sciatic nerve lesions in fractures of the pelvis has been reported in the literature as probably less than 1%. Yet for those who have become interested in fractures of the pelvis with involvement of the sciatic nerve, the situation resembles that with stress fractures. When you begin to look for this entity, the incidence increases to 9, 10, or 11%. Also, nobody really knows the incidence of peroneal palsy or paresis after fractures of the tibia or fibula, or both; we do know that it is fairly common, it is generally transitory, and it resolves itself with minimal or no residual effect. These comments are by way of introduction.

Dr. Ingvars J. Vittands:†

The first case is that of a 14-year-old boy who was pinned underneath an overturned tractor for an hour. At the time of the accident he had noted immediately that he was unable to move his left leg. He was brought to the emergency room where roentgenograms (Figure 1) were made. He was noted to be unable to dorsiflex his right foot, and there was numbness of the lateral aspect of his right calf and foot. A neurologic examination showed weakness of the psoas and hamstring muscles and marked weakness of the gastrocnemius, anterior and posterior tibial, peroneal, and foot flexor muscles; there was also decreased sensation on the lateral aspect of the right leg and dorsal and plantar aspects of the foot. A diagnosis of trauma to the sciatic nerve, especially to the peroneal division, was made.

Conference held May 15, 1968 at the Mayo Clinic.

*Associate Professor of Clinical Orthopedic Surgery, Mayo Graduate School of Medicine (University of Minnesota), Rochester, and Consultant, Section of Orthopedic Surgery, Mayo Clinic, Rochester.

†Resident in Orthopedic Surgery, Mayo Graduate School of Medicine.

Dr. Johnson:

In this case there has been disruption of the pelvis—the so-called pelvic ring is broken—and probably a dislocation in one sacro-iliac joint. The symphysis seems to be spread, and the superior and inferior rami are fractured. The patient has had a crushing injury of the pelvis and has a sciatic nerve lesion.

Dr. Vittands:

Subsequently, the neurologic deficit stabilized, and it turned out that most of the weakness of the proximal muscles in the leg was due to pain in the pelvis; mainly, there was weakness in the peroneal division. Serial electromyograms confirmed the lesion; on the last neurologic examination only the anterior tibial, toe extensor, and peroneal muscles were weak. There was a slight decrease in sensation on the anteromedial aspect of the foot. By three and a half years after the injury, his condition seemed to have become stable and there was no further neurologic improvement. He was still unable to dorsiflex his foot. He had a foot drop and wore a brace. He has been considered for arthrodesis of his foot or transplant of the posterior tibial tendons.

The next case also involves a victim of a tractor accident; the patient was a 28-year-old man who had sustained a fracture of the shaft of the left femur. Shortly after the accident he had noted that he was unable to dorsiflex his foot and that he had lost sensation on the lower part of his left leg. He had been treated elsewhere (traction and, subsequently, a long-leg cast) (Figures 2 A and B); however, when the cast was removed, it was noted that an ulcer had developed over his heel. He was referred to the Mayo Clinic (six months after the injury) and, on neurologic examination,

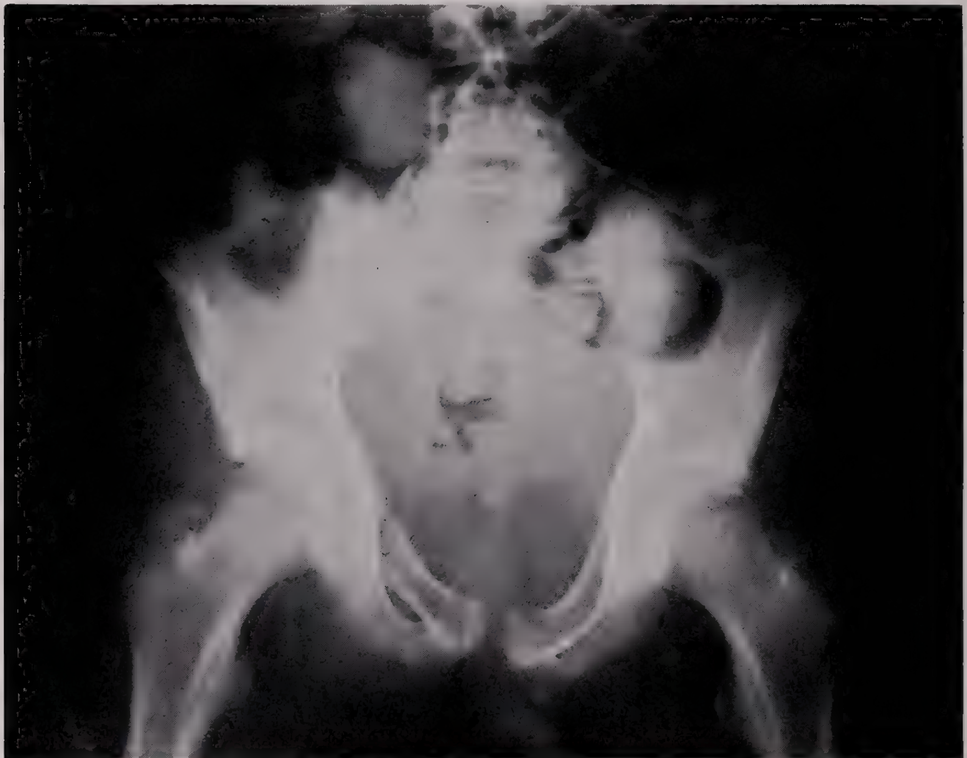

Fig. 1—(Case 1). Fractures of both pubic rami and dislocation of right sacro-iliac joint.

was found to have complete anesthesia of the sole and dorsilateral aspect of the foot and lateral aspect of the lower third of the leg. Ankle jerk was absent and there was essentially no movement at the ankle or toes. An electromyogram was consistent with a lesion of the sciatic nerve on the left side.

Dr. Johnson:

In this case there was a fracture at the junction of the middle and lower thirds of the femur and a sciatic nerve lesion; union was achieved after treatment with traction (elsewhere) with about two inches of shortening (Figures 2 C and D); but a sciatic nerve lesion was still evident when we saw him half a year after his accident. After extensive neurologic consultation, it was decided to explore the nerve; it was found to be divided and trapped in the scar tissue at the posterior aspect of the fracture. From a quick search of the literature, division of the sciatic nerve in the case of a fracture of the femur is rare; we have not been able to find another case.

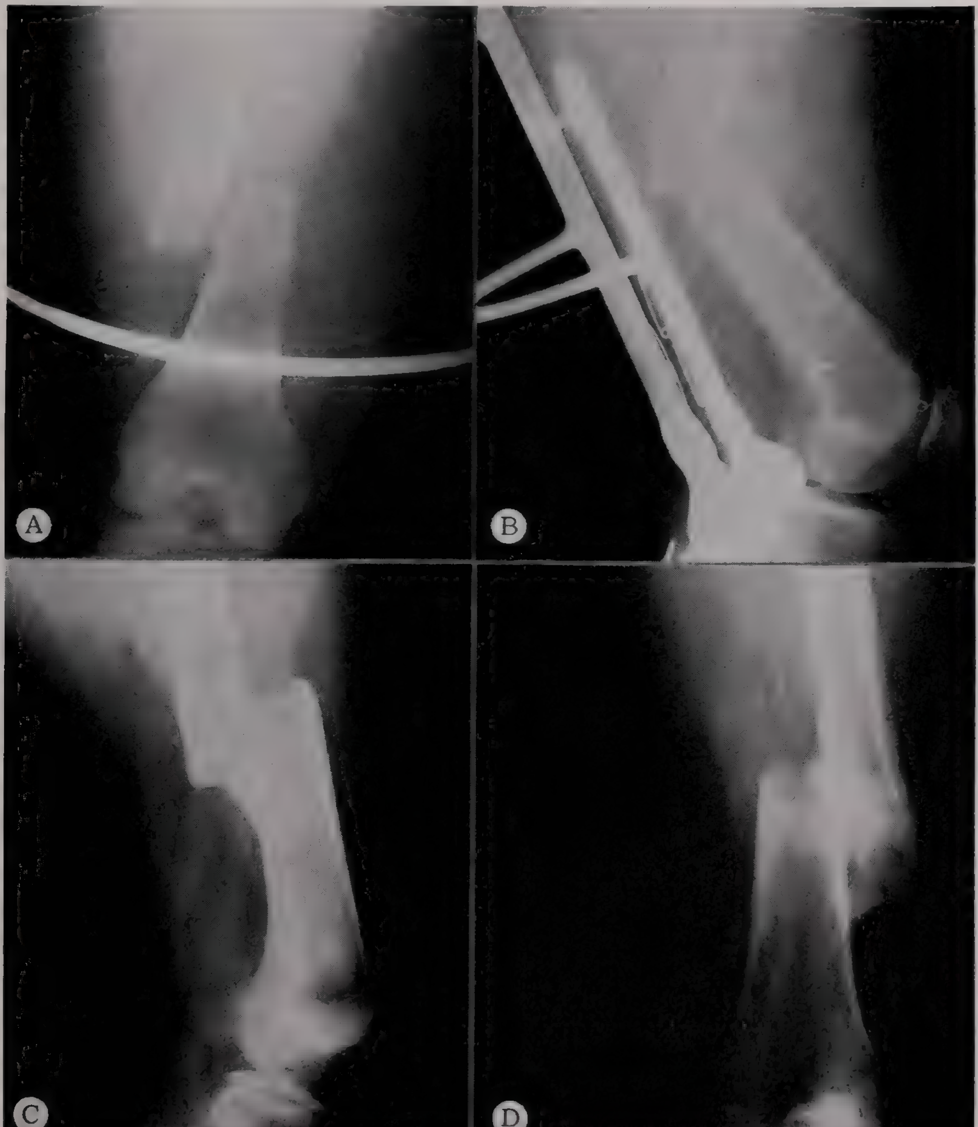

Fig. 2—(Case 2). Fracture of shaft of left femur. (A) and (B), In traction, shortly after original injury. (C) and (D), At admission at Mayo Clinic.

The nerve was repaired and we are waiting to see whether it will redevelop.

Dr. Vittands:

In the third case, a 20-year-old man sustained a crush injury of the tibia, which had been treated elsewhere with a cast. He had noted that he was unable to move his toes and that there was numbness of his foot at the time of injury. When the cast was removed 14 weeks later, he had painless ulcers on the posterior aspect of the right calf and over the right fifth metatarsal, as well as a foot drop. Sixteen months after the accident his right peroneal nerve had been explored (elsewhere) and the scar tissue around the nerve had been resected; however, there was no improvement. He was referred here for an indolent ulcer over the head of the fifth metatarsal of the right foot. On examination he was found to have a right foot drop and weakness of the anterior tibial, toe extensor, toe flexor, and peroneal muscles. Sensation was decreased on the sole and dorsal aspect of the foot and lateral aspect of the leg. A diagnosis of partial injury of the right peroneal and tibial nerves was made. The electromyogram was consistent with a lesion of the right peroneal nerve.

The Sciatic Nerve

These three cases illustrate lesions of the sciatic nerve caused by fracture and dislocation of the pelvis or bones of the lower extremity. Except for lesions of the common peroneal nerve, such injuries are relatively rare in a civilian practice. Only a few large series have been reported. In one report,[1] by the Medical Research Council in England, World War II injuries were analyzed. Woodhall[2] analyzed 7,050 nerve injuries and found that a quarter of them involved the sciatic nerve. Most of these, however, were not due to fractures and, in the study in England, only 6% were due to fractures primarily. Lewis and Miller[3] reviewed 253 fractures associated with nerve lesions and found eight involving the common peroneal nerve, one the sciatic nerve, and one the sacral plexus. Gurdjian and Smathers[4] reported on 53 nerve injuries; eight involved the peroneal nerve and one, the sciatic nerve. They concluded that the peroneal was the third most commonly injured nerve, after the radial and the ulnar nerves.

The sciatic nerve is particularly vulnerable at several points along its course; for this reason a brief review of its relationship is in order.[5] It derives from the sacral plexus, the last two lumbar and first three or four sacral nerves. The plexus itself lies against the posterolateral wall of the pelvis between the piriform muscle and the hypogastric vessels; from here it converges toward the greater sciatic notch to form the trunk of the nerve. In this location it is subject to injury in sacral and pelvic fractures, particularly the lumbosacral trunk which lies close to the posterior pelvic ring. After leaving the pelvis, the nerve lies on the posterior surface of the ischium between the ischial tuberosity and the greater trochanter muscle crossing the external rotators of the hip, where it can be injured in posterior dislocations of the hip. The posterior fragment of the acetabulum may stretch or lacerate the peroneal part of the nerve. More distally the nerve lies well protected on the adductor magnus under the biceps femoris and is injured here only very rarely.

Posterior Tibial Nerve

The two major divisions of the sciatic nerve are the peroneal and the posterior tibial. The posterior tibial nerve continues deep to the biceps femoris, crosses the popliteal fossa, passes between the heads of the gastrocnemius deep to the soleus, and finally divides into the medial and lateral plantar nerves. Thus it is well protected and rarely injured in ordinary fractures. The peroneal nerve runs along the lateral side of the popliteal fossa close to the medial border of the biceps femoris, winds around the neck of the fibula, and passes through the peroneal muscles, dividing into the superficial and deep peroneal nerves. It is thus quite exposed and accordingly the most frequently injured part of the sciatic nerve.

In 1961 Patterson and Morton[6] reviewed the neurologic complications of fractures and dislocations of the pelvis and reported on 15 cases of nerve injury found in 809 pelvic fractures. They concluded that their incidence, 1.2%, was low and would probably increase with the increasing awareness of this complication. In their series, 33% of cases also had associated sacral fractures, which they thought were frequently overlooked. They quoted Bonnin[7] who found that 24% of all pelvic fracture cases also included sacral fractures. The incidence of nerve injury is lower in pelvic fractures than in traumatic hip dislocations. Morton[8] found an incidence of 16% in the latter. Cave[9] reviewed the Massachusetts General Hospital series and found sciatic lesions in 12% of all cases of injured hips, all posterior dislocations of the hip. Among this type of hip injury these nerve injuries were found in 27% of cases. None of the series mentioned any sciatic nerve lesion due to fracture of the femoral shaft, such as in our second case.

Peroneal Nerve

Lesions of the common peroneal nerve are well known and occur after crush injuries and adduction injuries of the knee. Nobel[10] recently recorded two cases of peroneal lesions after spiral fractures of the distal tibia and fibula. Both cases were characterized by an unusual amount of pain and progressive neurologic deficits which were relieved by evacuation of the hematoma from the sheath of the common peroneal nerve. Oppenheim,[11] who reported on peroneal palsies after inversion sprains of the ankle, demonstrated on cadavers that pulling on the cutaneous branches of the superficial peroneal nerve could markedly displace the common peroneal nerve at the knee, making such injuries of the peroneal nerve possible.

Although the total incidence of injury to the sciatic nerve in civilian practice is low, the incidence in certain specific fractures and dislocations is high and should be suspected in such injuries. The possibility of an interneural hematoma should be suspected in tibial fractures and ankle injuries with an unusual amount of pain, especially if this pain is "neuritic" in nature and is associated with a neurologic deficit.

Dr. Johnson:

Thank you, Dr. Vittands. I think this issue is pretty much like the matter of stress fractures that we were speaking about earlier. If we do not think about it, we probably will not recognize it. It is not very hard to detect a foot drop if you ask the patient to dorsiflex his foot and toes. However, if you do find a foot drop, what do you do? Well, I imagine that, in Case 1—

a fracture-dislocation of the pelvis—there is not very much you can do except hope that the thing will resolve by itself. But the second case is a different matter. Dr. Laurnen, what do you think should have been done in Case 2?

Dr. Edwin L. Laurnen:[*]

It is a rare case. I think I would consider exploring the sciatic nerve at the level of the fracture in the femur. There is some controversy on this point.

Dr. Johnson:

What you say is that, because there is an obvious neurologic deficit, a foot drop, and a fracture, the nerve should be explored in Case 2. Is that right? Perhaps part of your decision might be based on whether or not the foot drop was immediate or came on slowly. If you could find out from the patient that his foot drop occurred immediately after the fracture, what would you do: explore the nerve, fix the fracture, or both?

Dr Laurnen:

I think you should do both at the same time.

Dr. Johnson:

I would think that this might be a lot of surgery at one time. I would say that, although this is not an ideal location, perhaps you should do an intramedullary fixation of this fracture and, if you have to open it up extensively, you could explore the nerve at the same time. But if not, then one should wait a few days, then go back posteriorly and explore the nerve if necessary. In any event, I think we can agree that in Case 2 the nerve should have been explored earlier instead of half a year later when the trophic[†] ulcer was already present on the heel, the patient already had the foot drop, and the fracture had united with two inches of shortening. As far as Case 3 is concerned, this patient was caught between rolling pieces of pipe, and the upper part of his tibia was crushed. He had an immediate foot drop and trophic ulcers on the calf, on the heel, and over the head of the fifth metatarsal when the cast was removed. So he probably had an immediate nerve lesion as well. I think the nerve should have been explored. It is hard to say how exploration could have been accomplished in this third case, because I suspect that the nerve was considerably traumatized. However, there is very little, if any, damage done to the nerve by gentle exploration as long as you do not strip its sheath, deprive it of its blood supply, or dislocate a lot of its surrounding and protective soft tissue. Surely this would solve the problem of deciding between division and trauma to the nerve. You have to wait three weeks to get any sensible beginning evidence for nerve loss by electromyography and so may lose three weeks of time.

Dr. William H. Bickel:[†]

I once had a case in which a boy had an undisplaced fracture of the junction of the middle and lower thirds of the tibia and subsequently lost the use of the muscle to his great toe, the extensor hallucis. It was out completely, but he had no other nerve injuries. Six months later, when the electromyogram showed that it was still out, the neurologist gave up and said it was not going to return. I was getting ready to fuse the interphalangeal joint of the great toe, because the boy was a swimmer and went around barefoot; but now, a year and a half later, the muscle is coming back. So the electromyogram is not completely reliable as far as return of the nerve is concerned.

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[*] Resident in Orthopedic Surgery, Mayo Graduate School of Medicine, Rochester.

[†] See Test Your Word Score Page 672.

[‡] Professor of Orthopedic Surgery, Mayo Graduate School of Medicine (University of Minnesota), Rochester, and Consultant, Section of Orthopedic Surgery, Mayo Clinic, Rochester.

Dr. Joseph M. Janes:*

Would you often wait 18 months to see the final results of a nerve lesion?

Dr. Johnson:

Full return may not be evident at 18 months. In the first case it has been more than that—three or four years. The patient's condition became stable in about three years. We recorded serial electromyograms every six months for several years.

I am sure one can see return of nerve function 18 months and later after nerve injury. And sometimes, as in our first case, it is wise to wait even longer.

In summary let me make these points:

1. Nerve injury is always possible in almost any fracture and should be looked for.
2. Immediate loss of nerve function often means division of the nerve, whereas gradual loss means partial loss due to swelling or encroachment. Immediate loss of function may be a reason for exploration of the nerve under selected circumstances, as in Case 2.
3. If the nerve has not been divided you can look for return of function for several months after injury, and sometimes several years.

Einer W. Johnson, Jr., M.D.†
Ingvars J. Vittands, M.D.†
Rochester, Minnesota

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†Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

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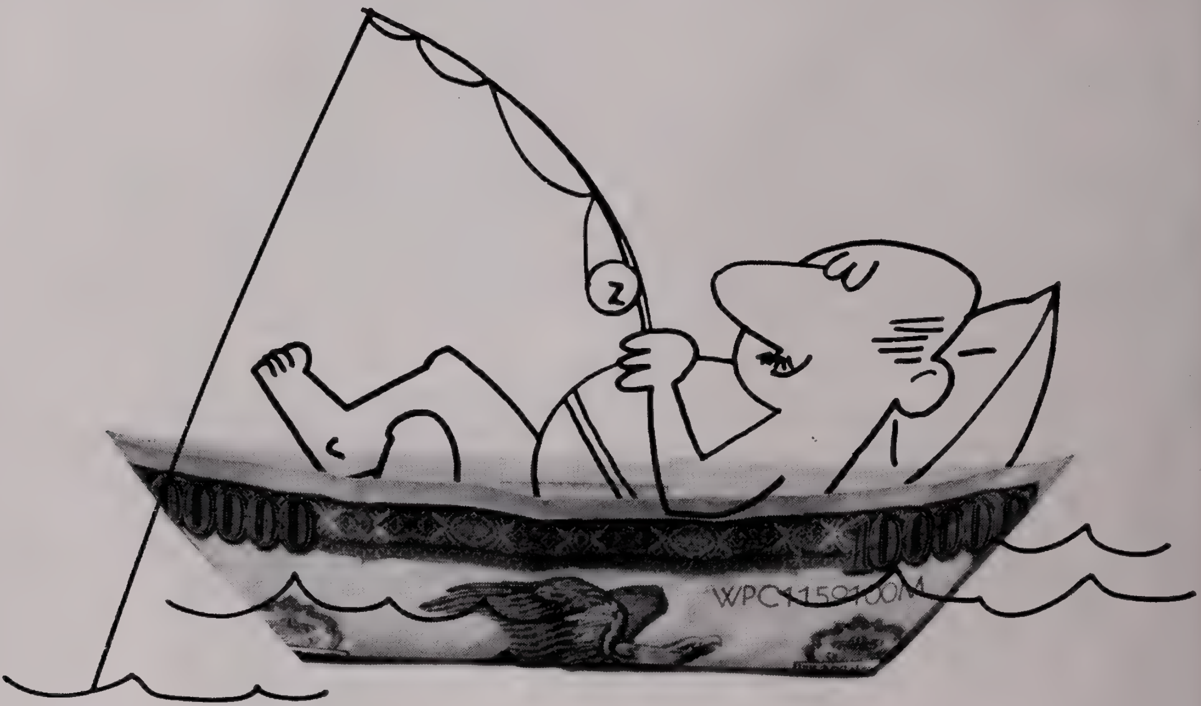
Wrinkles should merely indicate where smiles have been.—Mark Twain

It's nice to have enough money to retire on.



It's also nice to be around when it's time to retire.

You want to save a nest egg to retire on? Fine. All we suggest is that you be here to enjoy it. What to do? See your doctor for a thorough health checkup once a year, including a procto. And for women, also a Pap test. In short, the works.

Because most cancers are curable if spotted in time. But your doctor won't be able to spot anything—unless you give him the chance.

If you do, you'll improve your chances of enjoying your retirement. To a ripe old age.

american
cancer
society®

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Nose clear as a whistle

(THANKS TO DIMETAPP®)

Dimetapp Extentabs® does an outstanding job of helping to clear up the stuffiness, drip and congestion of colds and upper respiratory allergies and infections. Each Extentab keeps working up to 12 hours. And for most patients drowsiness or overstimulation is unlikely. Try Dimetapp. It clearly works.

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Dimetane® (brompheniramine maleate), 12 mg.; phenylephrine HCl, 15 mg.; phenylpropanolamine HCl, 15 mg.

FOR UPPER RESPIRATORY ALLERGIES AND INFECTIONS

Indications: Dimetapp is indicated for symptomatic relief of the allergic manifestations of respiratory illnesses, such as the common cold and bronchial asthma, seasonal allergies, sinusitis, rhinitis, conjunctivitis, and otitis.
Contraindications: Hypersensitivity to antihistamines. Not recommended for use during pregnancy.
Precautions: Until patient's response has been determined, he should be cautioned against engaging in operations requiring alertness. Administer with care to patients with cardiac or peripheral vascular diseases or hypertension.
Side Effects: Hypersensitivity reactions including skin rashes, urticaria, hypotension and thrombocytopenia, have been reported on rare occasions. Drowsiness, lassitude, nausea, giddiness, dryness of the mouth, mydriasis, increased irritability or excitement may be encountered.
Dosage: 1 Extentab morning and evening.
Supplied: Bottles of 100 and 500.

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Mild ulcerative colitis may be triggered here...

In mild ulcerative colitis, a number of factors can precipitate an attack: for instance, dietary indiscretion, such as eating raw foods, or emotional overreaction, such as that aroused by financial difficulties. No matter what causes the patient's sensitive colon to "act up," he soon suffers from acute discomfort...and often, from anxiety and apprehension as well. Such patients frequently respond well to adjunctive dual-action Librax® therapy.

Librax combines, in a single convenient capsule, the well-known antianxiety effect of Librium® (chlordiazepoxide HCl) and the dependable anticholinergic /antispasmodic effect of Quarzan® (clidinium Br). Therefore, as Librax helps to relieve the patient's excessive anxiety and reduce his overreaction to stress, it also, at the same time, helps to control hypersecretion and hypermotility, thus relieving spasm and abdominal discomfort.

With Librax, the dosage schedule is simple: 1 or 2 capsules, t.i.d. or q.i.d., will in most cases bring the patient significant relief of both the emotional and physical elements that contribute to his psychovisceral disorder.

Before prescribing, please consult complete product information, a summary of which follows.

INDICATIONS: Indicated as adjunctive therapy to control emotional and somatic factors in gastrointestinal disorders.

CONTRAINDICATIONS: Patients with glaucoma; prostatic hypertrophy and benign bladder neck obstruction; known hypersensitivity to chlordiazepoxide HCl and/or clidinium bromide.

WARNINGS: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering Librium (chlordiazepoxide hydrochloride) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards. As with all anticholinergic drugs, an inhibiting effect on lactation may occur.

PRECAUTIONS: In elderly and debilitated, limit dosage to smallest effective amount to preclude development of ataxia, oversedation or confusion (not more than two capsules per day initially; increase gradually as needed and toler-

or here.

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ated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

ADVERSE REACTIONS: No side effects or manifestations not seen with either compound alone have been reported with Librax. When chlordiazepoxide hydrochloride is used alone, drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally with chlordiazepoxide hydrochloride, making periodic blood counts and liver-function tests advisable during protracted therapy. Adverse effects reported with Librax are typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy and constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diet.

two good reasons for prescribing LIBRAX®

Each capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium Br.

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Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

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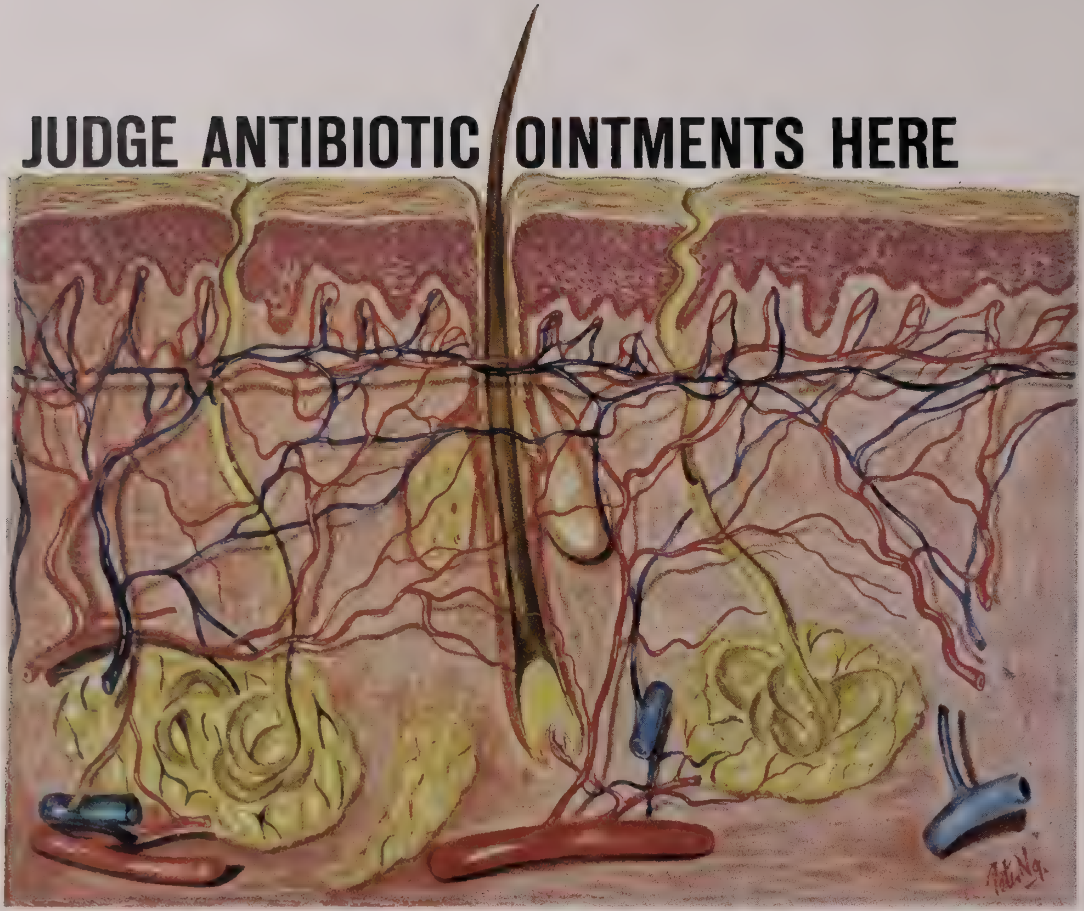

Results on skin are final proof of any topical antibiotic's effectiveness

No in vitro test can duplicate a clinical situation on living skin. 'Neosporin' (polymyxin B—bacitracin—neomycin) Ointment has consistently proven its effectiveness in thousands of cases of bacterial skin infection. The spectra of the three antibiotics overlap in such a way as to provide bactericidal action against most pathogenic bacteria likely to be found topically. Diffusion of the antibiotics from the special petrolatum base is rapid since they are insoluble in the petrolatum, but readily soluble in tissue fluids. The Ointment is bland and nonirritating.

Caution: As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms and/or fungi. Appropriate measures should be taken if this occurs. Articles in the current medical literature indicate an increase in the prevalence of persons allergic to neomycin. The possibility of such a reaction should be borne in mind.

Contraindications: This product is contraindicated in those individuals who have shown hypersensitivity to any of its components.

Supplied: Tubes of 1 oz., ½ oz. with applicator tip, and ⅛ oz. with ophthalmic tip.

Complete literature available on request from Professional Services Dept. PML.

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Tumor Conference

Hamartoma of the Liver in a Pregnant Woman*

To have a hamartoma† of the liver is uncommon. For a pregnant woman to have one is rare. For a pregnant woman to have a hamartoma of the liver, then to deliver a normal child, and finally to have the tumor resected after delivery has yet to be recorded. This is an account of such a case.

Case Report

A 20-year-old white woman, pregnant for the first time, was seen at our clinic on September 11, 1964. Her last menstrual period had been July 1. On examination, she was about two and one-half months pregnant. The physical was otherwise normal, and laboratory work—hemoglobin, serological test for syphilis, Papanicolaou smear—and a chest film were also normal.

In her fourth month of pregnancy, the patient was in an automobile accident, but she was not seriously injured.

At 34 weeks of gestation, she noted a mass in the upper abdomen. We palpated it,

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*Presentation to the Minnesota Obstetrical and Gynecological Society, Duluth, Minnesota, May 6, 1967.

†See Test Your Word Score Page 672.

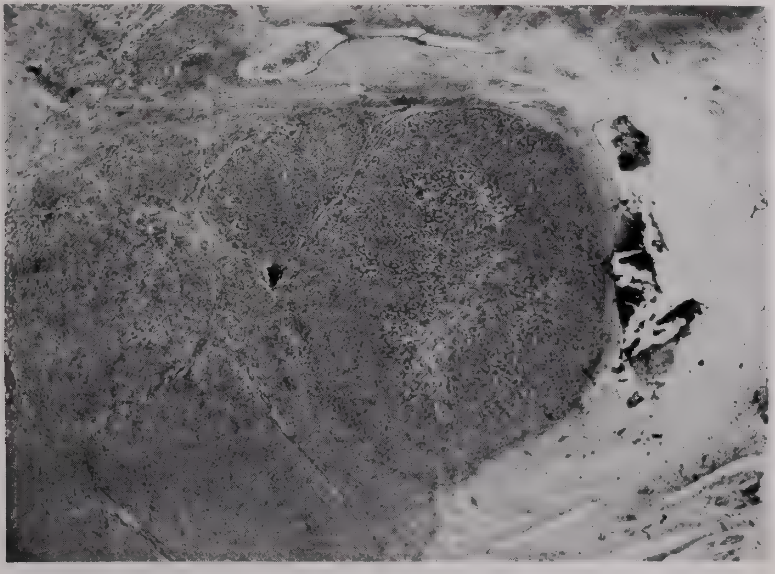

Fig. 1-A.—View showing nodularity, radiating striae of fibrous tissue, and loss of normal architecture.

and it felt like a nodular hard round 10-cm mass over the liver. It was our opinion that it might be a fibroid extending upward from the uterus, and we decided to let her go to term.

In her last trimester, she had mild preeclampsia with a 2+ albuminuria and a blood pressure of 144/100. We hospitalized her, induced labor with oral Pitocin, and ruptured the membranes. She delivered a normal seven-pound, one ounce girl.

After delivery, we could not palpate the tumor when the patient was supine. But when she stood and leaned forward, we could delineate a hard mass which was not connected to the uterus.

A flat plate of the abdomen, intravenous pyelograms, an upper gastrointestinal series, a barium enema, and blood and urine tests were of no help in localizing the tumor (Figures 1-A, B and C). One radiologist ventured the opinion that it might be a mesenteric cyst. Because of our uncertainty about the diagnosis, we performed a laparotomy. Arising from the anterior aspect of the left lobe of the liver was a 10-cm lobulated mass. We excised the tumor and a wedge of surrounding liver.

After operation she did well and was discharged one week later. She is now in good health, active, and has no complaints.

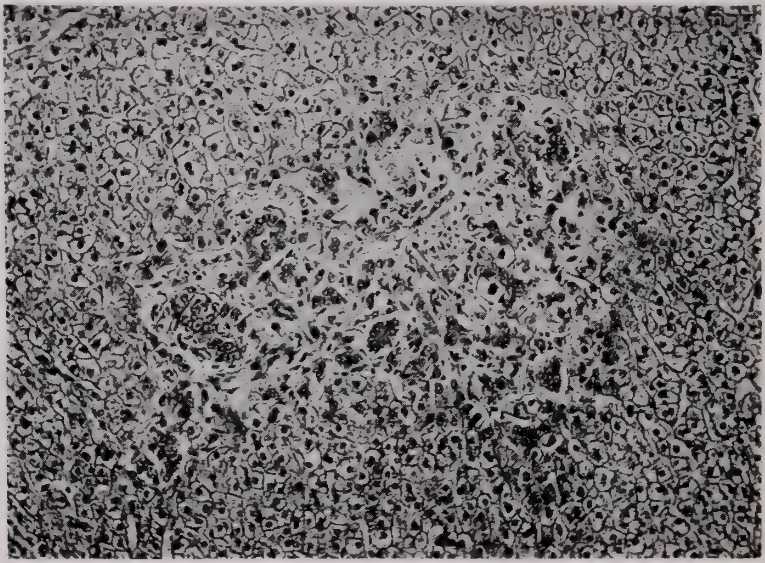

Fig. 1-B—View showing hyperplasia of the bile ducts.

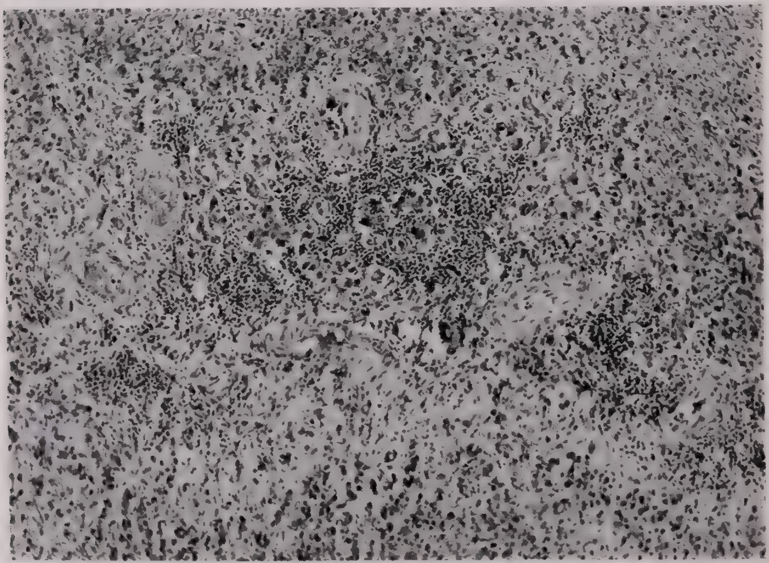

Fig. 1-C—View showing infiltration of leukocytes, indicative of pericholangitis.

Pathological Findings

The pathologist's report read as follows: "Specimen from the left lobe of the liver is an irregular, lobular mass, 9x8x5 centimeters over all. On one margin there is a segment of hepatic tissue of normal appearance over a zone of about 7x1.5 centimeters which appears to be the plane of the polypoid mass. On section the mass is rather finely nodular and has essentially the appearance of a cirrhotic liver." Microscopically, he described fibrous septa which divided liver tissue into irregular islands. The small bile ducts were proliferating, and many of them were not related to the portal triads. He also noted prominent venous channels and pericholangitis. He concluded his report by saying he thought the mass was most likely a hamartoma.

Comment

Although Kiser et al. have reported a hamartoma of the kidney in a pregnant woman,[1] we are not aware of any accounts of hepatic hamartoma in pregnancy. Liver disease of any kind is unusual in pregnancy. Some women develop a cholestatic jaundice late in their gestation; others may contact hepatitis if exposed; and a rare patient may have cirrhosis. Fulminating eclampsia can produce necrosis in the liver.

A hamartoma is a tumor composed of an abnormal mixture of normal constituents of an organ. Benz and Baggenstoss[2] believe that hamartomas of the liver, benign hepatomas, solitary hyperplastic nodules, focal cirrhosis, adenomas, and cholangiohepatomas strongly resemble each other, and may, indeed, represent the same lesion. They reviewed 24 recorded cases of adenomas and hamartomas. Ages of patients ranged from seven months to 88 years. Then they gathered 34 more cases from their autopsy files. Ages varied from 27 to 74 years. All lesions were incidental, and none had caused symptoms. Most lesions arose from the right lobe of the liver. The largest was 5.5 cm; the smallest 0.3 cm; the average 1.2 cm.

Of the 34 livers (40 lesions) they studied histologically, they considered only two true adenomas. These two had no bile ducts, portal triads, or inflammatory cells. Most lesions had bile ducts. Kay and Talbert have emphasized that bile ducts often proliferate in hamartomas.[3]

Anderson[4] describes liver hamartomas as cystic and gray-white to red-purple. He says they usually spring from the lower margin of the right lobe of the liver before two years of age. They grow rapidly because they accumulate fluid. Microscopically, acellular collagenous connective tissue cells often predominate, and remnants of bile ducts and fluid-filled spaces occur.

Summary

A 20-year-old woman observed an abdominal mass in the 34th week of pregnancy. After she delivered a normal girl, a laparotomy was done, and a 9-cm hamartoma was resected from the left lobe of the liver. The patient is active and in good health nearly three years after the tumor was removed.

Charles A. Field, M.D.*
Rochester, Minnesota

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*Department of Obstetrics and Gynecology, Olmsted Medical Group, Rochester, Minnesota.

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3-4. May be secured from the author or the reprints.

in cerebrovascular disorders

Arlidin increases blood flow

Arlidin decreases cerebral vascular resistance, increases cardiac output, helps maintain mean arterial pressure.

Arlidin helps control vasoconstriction, vasospasm, and ischemia.

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Arlidin is well tolerated and relatively free of severe adverse reactions.

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SUPPLIED: Tablets, 6 mg., scored; bottles of 100 and 1000. Parenteral, 5 mg. per cc., 1 cc. ampuls (5 per box); 10 cc. multiple-dose vials (1 per box). CONSULT PRODUCT BROCHURE.

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DECREASES
ARTERIAL
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Laboratory Letter

Wall Chart of Abnormal Values

For busy physicians, diagnosing disease ought to be an act of judgment, not a feat of memory. But for this to be so, you must have readily accessible information at your fingertips or in your range of vision. This wall chart, listing conditions that cause high or low values for certain chemistry tests, should help you rapidly sort through diagnostic possibilities when you receive an abnormal result.

Richard L. Reece, M.D.
Minneapolis, Minnesota

SMA—12/60 WALL CHART

Tests in Same Numerical Order as Those on Graph (See M.M.)

I

Elevated Values of Serum Calcium

- Hyperparathyroidism
- Hypervitaminosis D
- Multiple myeloma
- Prolonged immobilization
- Sarcoidosis
- Secondary carcinomatosis involving bone
- Certain neoplasms, even without demonstrable bone metastases
- Leukemia
- Milk-alkali syndrome
- Idiopathic hypercalcemia of infancy
- Hyperthyroidism (rarely)

Decreased Levels of Serum Calcium

- Hypoparathyroidism
- Osteomalacia
- Steatorrhea
- Acute pancreatitis
- Renal insufficiency (phosphorus increased)
- Vitamin D deficiency
- Renal tubular acidosis

II

Elevated Serum Phosphorus

- Children (4-6 mg.%)
- Renal insufficiency
- Diabetic acidosis
- Acromegaly
- Hypoparathyroidism
- Hemolysis

Decreased Serum Phosphorus

- Primary hyperparathyroidism
- Osteomalacia
- Renal tubular disorders (Fanconi syndrome)
- Use of certain antacids which bind phosphorus
- After insulin or large carbohydrate meal.

III

Elevated Levels of Glucose

- Diabetes mellitus
- Some cases of adrenal, pituitary, or thyroid hyperactivity
- Some cases of sepsis, tumors, and anoxia
- Pheochromocytoma

III (Continued)

Increased intracranial pressure
Nephrosis
Thiazide diuretics, corticoids, and nicotinic acid
Recent or current IV infusions of glucose

Decreased Levels of Glucose

Excessive insulin administration
Pancreatic islet cell tumors (insulinomas)
Myxedema
Glycogen storage disease
Leucine-sensitive hypoglycemia in infants
Certain large fibromas, sarcomas and carcinomas
Adrenal cortical insufficiency
Congenital adrenal hyperplasia
Adenohypophysial hypofunction
Diseases of the liver
After starvation, prolonged exercise, lactation, diarrhea, renal glycosuria
"Functional or reactive" hypoglycemia
Therapy with sulfonylureas, amino acids, and ganglionic blocking agents.

IV

Elevated Values of Bun

Renal insufficiency
G. I. bleeding
Lower urinary tract obstruction
"Pre-renal" azotemia from shock, dehydration, diarrhea, diabetic coma, heart failure

Decreased Values of Bun

Severe liver impairment
Normal pregnancy
Decreased protein intake
Excessive intravenous fluids

V

Elevated Values of Uric Acid

Gout
Renal failure
Toxemia of pregnancy
Excessive destruction of cells—lymphoma, leukemia, hemolytic anemia, resolving pneumonia, polycythemia, myeloma, pernicious anemia, infectious mononucleosis
Use of thiazides, acetazolamide, and low doses of salicylates
Certain cases of hypertension
Starvation
Violent muscular exercise
X-linked primary hyperuricemia
Diabetic acidosis
Ethanol intoxication
Certain types of glycogen storage disease
Psoriasis

Decreased Values of Uric Acid

Rare except after probenacid, high doses of salicylates, and allopurinol

VI

Elevated Values of Serum Cholesterol

Normal pregnancy
Nephrotic syndrome
Hypothyroidism
Hypophysectomy
Pancreatitis
Diabetes mellitus
Primary of familial hypercholesterolemia

Decreased Values of Total Cholesterol

Hyperthyroidism
Hepatic disease
Tangier disease
Abeta-lipoproteinemia
Malnutrition and malabsorption

VII

Decreased Albumin

Malnutrition
Cirrhosis
Hepatic disease—hepatitis, cirrhosis
Nephrotic syndrome
Supine position

Increased Albumin

Dehydration

VIII

Increased Globulin*

Infection
Liver disease
Malnutrition
Neoplasms, especially multiple myeloma
Dysproteinemias (macroglobulins and cryoglobulins)
Hypersensitivity states
"Collagen diseases"
Granulomatous diseases (sarcoidosis, etc.)

Decreased Globulin

Congenital or acquired hypogammaglobulinemia
Some granulomatous diseases

*NOTE—Globulin equals total protein minus albumin

IX

Elevated Values of Total Bilirubin

Neonatal jaundice
Erythroblastosis
Crigler-Najjar syndrome
Gilbert's disease
Dubin-Johnson syndrome
Hemolytic anemia
Intra- or extra-hepatic biliary obstruction
Cirrhosis
Hepatitis (viral, toxic, etc.)

X

Elevated Values of Alkaline Phosphatase

Children up to puberty
Healing of a fracture
Bone metastases
Rickets
Paget's disease (high levels in active disease)
Hyperparathyroidism (specially when the diet is deficient in calcium)
Biliary obstruction due to stones or neoplasm
Metastatic tumor to the liver
Cirrhosis
Hepatitis
Congestive heart failure
Pulmonary infarction (The elevation is maximal 1 to 3 weeks after pulmonary embolism
Normal pregnancy (elevations are found especially during the last trimester; these values return to normal within 2 to 6 weeks postpartum). Higher values of serum alk. phosphatase are noted in preeclampsia than in normal pregnancy.

Decreased Alkaline Phosphatase

Hypophosphatasia (an inborn error of metabolism in which alkaline phosphatase is deficient in all body tissues)
Pernicious anemia (patients with pernicious anemia may have a relative decrease in serum alkaline phosphatase with a return to normal levels with B12 treatment).

XI

Elevated Levels of Serum LDH

Hemolysis
Myocardial infarction (the SGOT)
Pulmonary infarction (usually elevated)
Leukemia, lymphoma, carcinoma
Renal infarction
Seizures
Therapy with nicotinic acid
Pancreatitis
Sickle call anemia
Pernicious anemia
Collagen disease

XII

Elevated Values of SGOT

Hemolysis
Myocardial infarction (the SGOT usually rises 6-12 hours after mycardial infarction, reaches a peak at 24 to 28 hours and returns to normal in 4-7 days.
Congestive failure (due to central lobular necrosis of the liver)
Dicumerol therapy
Pericarditis
Myocarditis
Alcoholic myopathy (CPK also elevated)
Hepatitis
Muscle disease including muscular dystrophy, dermatomyositis, and gangrene
Trauma, including surgical trauma
Convulsions (will elevate both LDH and SGOT)
Renal infarction
Acute pancreatitis
Hemolytic anemias
Toxemia of pregnancy (extremely high levels are obtained after convulsions)

Karl Marx—Utopia

Karl Marx wrote: "In a Communist society where nobody has one exclusive sphere of activity, but each can become accomplished in any branch he wishes, society regulates the general production and thus makes it possible for me to do one thing today and another tomorrow, to hunt in the morning, fish in the afternoon, rear cattle in the evening, criticize after dinner, just as I have in mind, without ever becoming hunter, fisherman, shepherd or critic."

Marx was an escapist. He wanted to flee from time, scarcity, and earthly limitations. His economic analysis was directed at this world and therefore totally critical; his hopes for the future were Utopian and unrealistic.*

---

*Gary North, The Freeman, January 1969.

An Englishman thinks seated; a Frenchman, standing; an American, pacing; an Irishman, afterward.—Austin O'Malley

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The short skirts of today reveal the malnutrition of yesterday.—Don Herold

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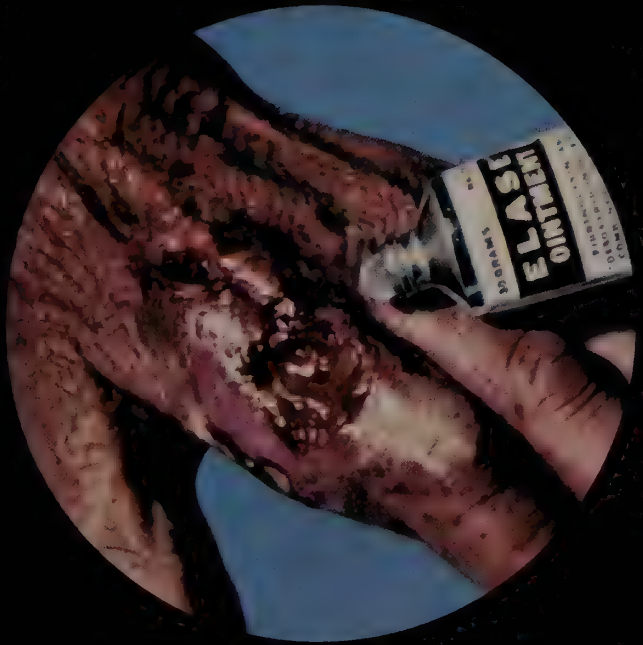
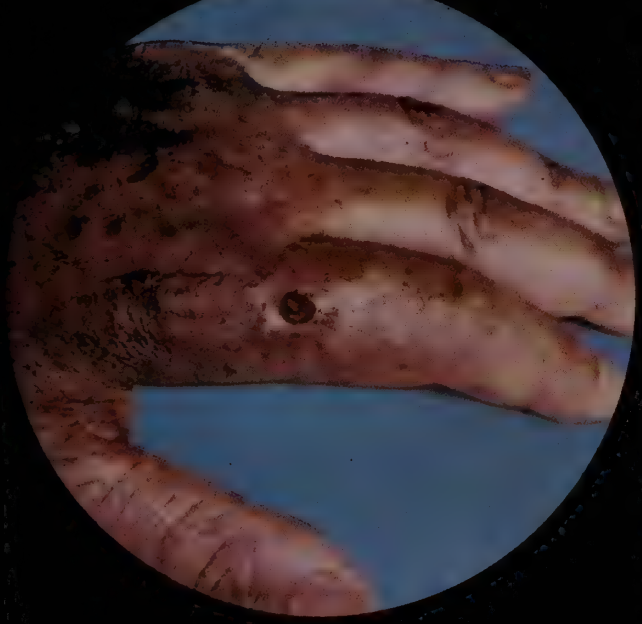
Kindness goes a long way lots of times when it ought to stay at home—Frank Hubbard

this ulcer did not heal...until its surface was cleared of dead tissue and debris



FIRST APPLICATION
ELASE Ointment is applied to a deep ulceration of a finger.

EIGHTEEN DAYS LATER
Healing has progressed rapidly without interruption or interference from any accumulated purulence or necrotic tissue. Greatly reduced size of lesion and minimal scar tissue indicate quality and vigor of healing which is almost complete.



to aid in debridement
to facilitate healing
in chronic cutaneous ulcers...

Elase® Ointment

(fibrinolysin and desoxyribonuclease, combined, [bovine] ointment)

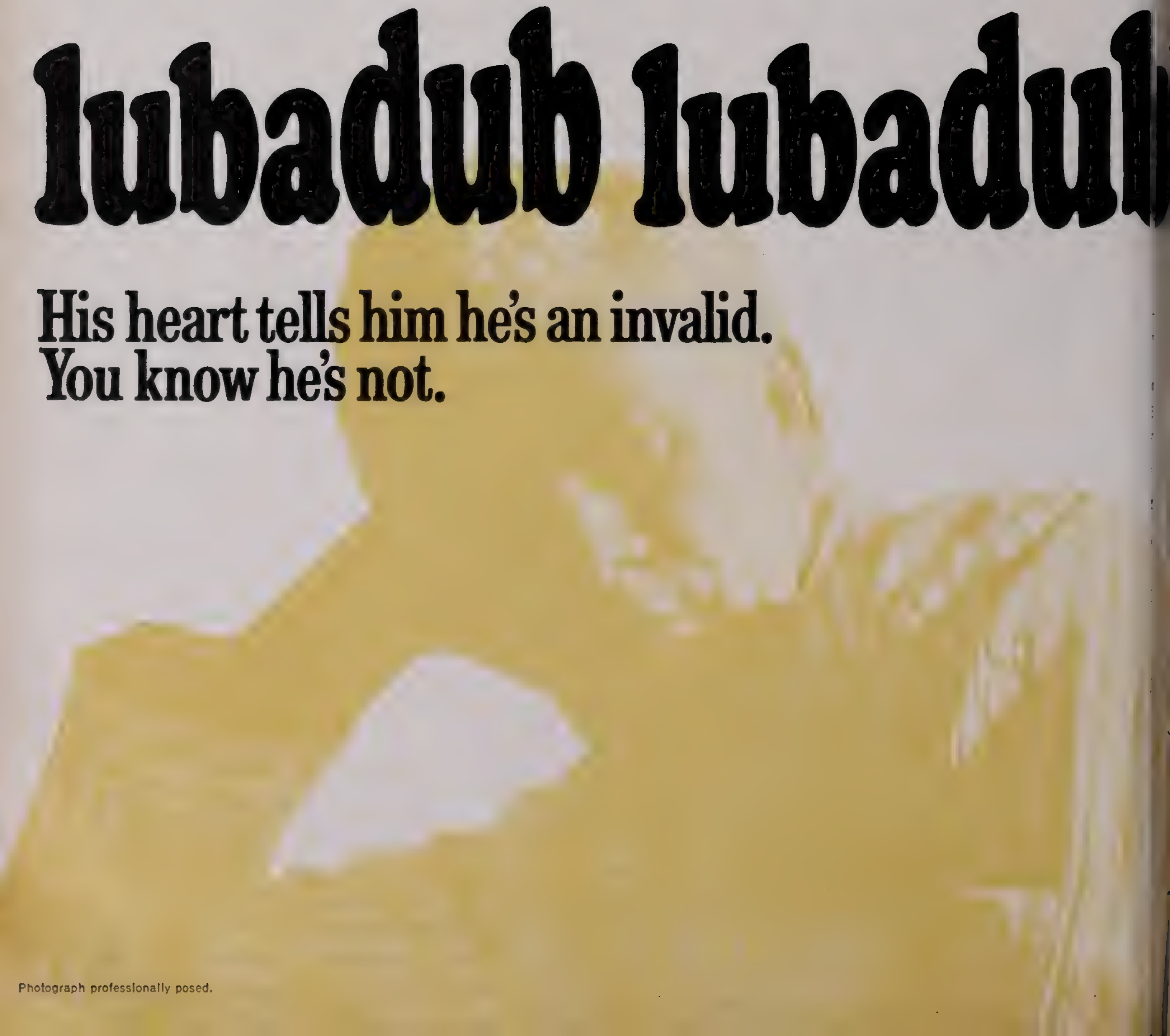
PARKE-DAVIS

By helping to remove dead tissue and debris from the ulcer's surface, ELASE Ointment creates a better environment for the elimination of infection, for healthy granulation...*for healing.* Its lytic enzymes effectively break down DNA in dead leukocytes and other debris...the fibrin in blood clots, serum, and purulent exudates...and the denatured proteins in necrotic tissue. Protein elements of *living* tissue are relatively unaffected. ELASE Ointment is indicated in stasis ulcers and in other infected or inflamed ulcers caused by circulatory disturbances. In cases requiring skin grafting, it is used preoperatively for debridement. For ambulatory patients debridement with ELASE Ointment is a convenient therapy and a regimen likely to be followed. *Precautions:* Observe usual precautions against allergic reactions, particularly in persons with a history of sensitivity to materials of bovine origin or to mercury compounds. *Adverse Reactions:* Side effects attributable to the enzymes have not been a problem at the dose and for the indications recommended. *Discussion:* Successful use of enzymatic debridement depends on several factors: (1) dense, dry eschar, if present, should be removed surgically before enzymatic debridement is attempted; (2) the enzyme must be in constant contact with the substrate; (3) accumulated necrotic debris must be periodically removed; (4) the enzyme must be replenished at least once daily; and (5) secondary closure or skin grafting must be employed as soon as possible after optimal debridement has been attained. It is further essential that wound-dressing techniques be performed carefully under aseptic conditions and that appropriate systemically acting antibiotics be administered concomitantly if, in the opinion of the physician, they are indicated. *Available:* ELASE Ointment is supplied in 30-Gm. tubes containing 30 units (Loomis) of fibrinolysin and 20,000 units of desoxyribonuclease with 0.12 mg. thimerosal (mercury derivative); and in 10-Gm. tubes containing 10 units of fibrinolysin and 6,666 units of desoxyribonuclease with 0.04 mg. thimerosal. ELASE Ointment has a special base of liquid petrolatum and polyethylene; contains sodium chloride and sucrose used during manufacture; is stable at room temperature through the expiration date stated on the package.

Parke, Davis & Company, Detroit, Michigan 48232

PARKE-DAVIS

46168


lubadub lubadul
His heart tells him he's an invalid.
You know he's not.

Photograph professionally posed.

badubdub lubad

Anxiety is expected in the cardiovascular patient. A little may even be desirable.

But when anxiety is exaggerated . . . when it nterferes with sleep . . . when it aggravates cardiovascular symptoms, your help may be needed.

Naturally, you'll want to reassure the patient.

And perhaps prescribe Equanil (meprobamate) as adjunctive therapy. It helps relieve anxiety and tension specifically, yet gently.

Almost 15 years' use has shown that Equanil s usually well tolerated as well as effective. Side effects are generally limited to transient drowsiness; serious, therapy-interrupting side effects are rare.

Contraindications: History of sensitivity to meprobamate.

Important Precautions: Carefully supervise dose and amounts prescribed, especially for patients prone to overdose themselves. Excessive prolonged use has been reported to result in dependence or habituation in susceptible persons, as alcoholics, ex-addicts, and other severe psychoneurotics. After prolonged excessive dosage, reduce dosage gradually to avoid possibly severe withdrawal reactions. Abrupt discontinuance of excessive doses has sometimes resulted in epileptiform seizures.

Warn patients of possible reduced alcohol tolerance, with resultant slowing of reaction time and impairment of judgment and coordination.

Reduce dose if drowsiness, ataxia or visual disturbance occurs; if persistent, patients should not operate vehicles or dangerous machinery.

Side Effects include drowsiness, usually transient; if persistent and associated with ataxia, usually responds to dose reduction; occasionally concomitant CNS stimulants (amphetamine, mephentermine sulfate) are desirable. Allergic or idiosyncratic reactions are rare, but such reactions, sometimes severe, can develop in patients receiving only 1 to 4 doses who have had no previous contact with meprobamate. Previous history of allergy may or may not be related to incidence of reactions. Mild reactions are characterized by itchy urticarial or erythematous maculopapular rash, generalized or confined to groin. Acute nonthrombocytopenic purpura with cutaneous petechiae, ecchymoses, peripheral edema and fever have been reported. One fatal case of bullous dermatitis following intermittent use of meprobamate with prednisolone has been reported. If allergic reaction occurs, meprobamate should be stopped and not reinstituted. Severe reactions, observed very rarely, include angioneurotic edema, bronchial spasms, fever, fainting spells, hypotensive crises (1 fatal case), anaphylaxis, stomatitis and proctitis (1 case) and hyperthermia. Treat symptomatically as with epinephrine, antihistamine and possibly hydrocortisone. Aplastic anemia (1 fatal case), thrombocytopenic purpura, agranulocytosis and hemolytic anemia have occurred rarely, almost always in presence of known toxic agents. A few cases of leukopenia, usually transient, have been reported on continuous administration.

Meprobamate may sometimes precipitate grand mal attacks in patients susceptible to both grand and petit mal. Extremely large doses can produce rhythmic fast activity in the cortical pattern. Impairment of accommodation and visual acuity has been reported rarely. After excessive dosage for weeks or months, withdraw gradually (1 or 2 weeks) to avoid recurrence of pretreatment symptoms (insomnia, severe anxiety, anorexia). Abrupt discontinuance of excessive doses has sometimes resulted in vomiting, ataxia, tremors, muscle twitching and epileptiform seizures. Prescribe very cautiously and in small amounts for patients with suicidal tendencies. Suicidal attempts have resulted in coma, shock, vasomotor and respiratory collapse and anuria. Excessive doses have resulted in prompt sleep; reduction of blood pressure, pulse and respiratory rates to basal levels; and occasionally hyperventilation. Treat with immediate gastric lavage and appropriate symptomatic therapy. (CNS stimulants and pressor amines as indicated.) Doses above 2400 mg./day are not recommended.

Composition: Tablets, 200 mg. and 400 mg. meprobamate. Coated Tablets, WYSEALS® EQUANIL (meprobamate) 400 mg. (All tablets also available in REDIPAK® [strip pack], Wyeth.) Continuous-Release Capsules, EQUANIL L-A (meprobamate) 400 mg.

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A little sunshine for summer cold and allergy sufferers.

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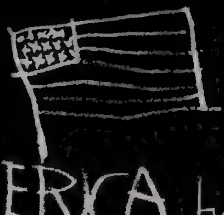
Litter is not pretty.
Litter is not Healthy.
Litter is not clean.
Litter is not American.
William Mahoney

Litter Is Something People shouldnt Do.
signed Suzie McGuire

litter is nasty.
Willie Warner

litter is what Bad people do
Pattie Wight

Litter is ugly and ~~dangos~~ ~~danjerus~~ bad.
Tommy Maltby



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Pityriasis Rosea

In 1860 Gibert described pityriasis rosea, an acute papulosquamous dermatosis. The disease affects males and females equally, and it is more common between the second and fifth decades. The cause is unknown. The disorder shows seasonal variations (spring and fall), causing speculation as to a viral nature. However, to date there is no proof of this.

Clinical

In a majority of cases the eruption begins with an isolated lesion (herald* or mother patch), usually located on the neck, trunk, or elsewhere. The primary lesion is pink and scaly and resembles tinea corporis. The herald plaque may not always be evident; sometimes it has regressed when the physician sees the patient.

Approximately seven to 10 days after the appearance of the primary lesion, the general eruption occurs. These lesions are usually macular, maculopapular or papular with little or no infiltration. Color varies from yellowish-red to scarlet. Individual lesions range from ½ to 3 cm. in diameter, although

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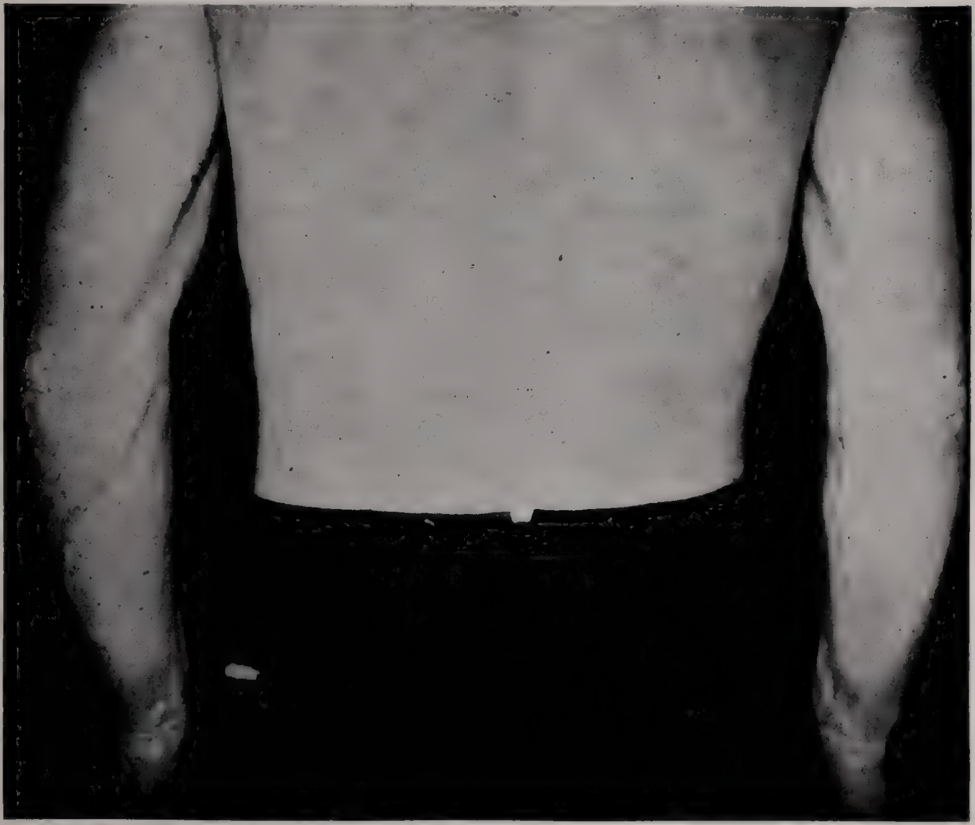
*See Test Your Word Score Page 672.



Figure

1 cm. is most common (smaller than the herald patch). There is a fine adherent collarette of scale at the periphery. The lesions enlarge by peripheral extension, leaving a clear center.

Distribution of the eruption is helpful in diagnosis. It usually affects the upper trunk; if more extensive, there are lesions on the proximal extremities. Involvement of the head, hands, lower legs, and feet is rare. On the trunk the long axis of the lesion follows the lines of cleavage and presents a characteristic appearance (Figure). Variations may occur, such as unilateral involvement, oral lesions, etc.

The most important general symptom is pruritus which varies from insignificant to severe and is usually worse at night and after a hot bath. Occasionally, fever, congestion of the fauces, and submaxillary and cervical adenitis occur. The disease usually runs a self-limited course of four to eight weeks. Secondary eczematization is an uncommon complication.

Differential Diagnosis

Macular syphilid, seborrheic dermatitis, psoriasis, and tinea corporis enter into the differential diagnosis. In macular syphilid the lesions are smaller and less scaly. Mucous membrane lesions, general adenopathy, and positive serologic tests are other signs of secondary syphilis. Seborrheic dermatitis commonly occurs on the scalp, central face, sternum, and intertriginous areas. The lesions usually have a greasy scale. In psoriasis the eruption has more infiltration, abundant silvery adherent scales, and a predilection for extensor surfaces. Tinea corporis is neither as extensive nor symmetric as pityriasis rosea. The lesions are larger and show more active inflammation at the border. Culture or examination with potassium hydroxide may be necessary for differentiation in some cases.

Treatment

Treatment consists of topical hydrocortisone lotions, creams, or ointments. If itching is severe, oral antihistamines are of value. Avoid anything which heats the skin (hot baths, exercise, etc.). If there is any question regarding diagnosis, serologic tests for syphilis should be performed.

Willard C. Peterson, Jr., M.D.
Minneapolis, Minnesota

Specialization

Specialists as a class are exposed to a particular set of dangers including those of the narrowness and monotony of "piece worker," those of loss of adaptability, those of objectionable aggressiveness, those of stubborn opinionatedness, those of boastful self-sufficiency, those of selfish materialism, and those of vanity and arrogance.*

---

*Barker, L. F., in Richard Magraw: Ferment in Medicine, 1966.

The worst jolt most of us ever get is when we fall back on our own resources.—Frank McKinney Hubbard

The Good, the True, the Beautiful! Alas, the Good is so often untrue, the True so often unbeautiful, the Beautiful so often not good.—Isaac Goldberg

Grand Rounds

Lactic Acidosis*

Erik E. Carlson, M.D.
Minneapolis, Minnesota

LACTIC ACID, an important product of normal glycogen metabolism, was first discovered in increased amounts in peripheral blood, following strenuous exercise, by Ryffel in 1909.[1] Barr, Himwich and Green studied the metabolic acidosis associated with exercise in 1923 and found elevated blood lactic acid concentrations.[2]

Clausen, in 1925, discussed the acidosis of anhydremia: a clinical syndrome then characterized by the "acute loss of fluid by diarrhea and vomiting in a previously well nourished person." He found elevated levels of blood lactic acid in the metabolic acidosis associated with both cardiac decompensation and anhydremia. Clausen linked this elevation of lactic acid to both inadequate circulation and/or reduced oxidative processes in the body and recommended that lactic acidosis was best treated by relief of the underlying circulatory condition.[3]

Sporadic references were made in the literature in subsequent years to lactic acidosis in association with a variety of disease states. However, it was not until Huckabee's initial report in 1961 of nine patients with lactic acidosis that this was felt to be of clinical significance.[4,5]

Lactic Acid Production

Glycogen (or glucose via glucose-6-phosphate) is normally metabolized to pyruvic acid in the first stage of carbohydrate dissimilation.[6] This process may occur under both aerobic and anaerobic conditions.

In the presence of *adequate oxygen* little lactic acid is formed. Rather, the pyruvic acid is broken down to CO_2, H_2O, and the reduced coenzyme 1 ($DPNH_2$) is reoxidized to diphosphonucleotide to again act as a hydrogen acceptor in stage one dissimilation.

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*Presented as a Medical Grand Rounds at Hennepin County General Hospital, Minneapolis, September 5, 1967.

Under *anaerobic* conditions pyruvate acts as a temporary hydrogen acceptor and oxidizes (dehydrogenates) the $DPNH_2 \rightarrow DPN$. In the process pyruvic acid is converted to lactic acid under the mediation of the enzyme lactic dehydrogenase according to the following equation:

(1) Pyruvate + $DPNH_2 \rightleftarrows$ Lactate + DPN

If we rewrite this equation (1) in its mass action form, we obtain the following:

$$(2)\ \{\text{Lactate}\} + \{\text{Pyruvate}\} \times K \frac{\{DPNH_2\}}{\{DPN\}}$$

Clearly then the direction of this reversible reaction depends upon the relative concentrations of the factors involved, i.e., pyruvate, lactate, diphosphonucleotide, $DPNH_2$ and lactic dehydrogenase. Huckabee[7] suggests that on a theoretical basis lactate production may be considered to reflect three situations:

(A) Relative inadequacy of oxygen supply with regard to metabolic needs,

which is expressed by $K \frac{\{DPNH_2\}}{\{DPN\}}$

(B) Changes in pyruvate concentration

(C) Changes in both factors simultaneously.

Experimentally, Huckabee found that the infusion of bicarbonate, glucose, pyruvate and hyperventilation in both humans and animals would produce a change in blood lactate concentrations in the absence of any detectable hypoxia on the basis of arterial and mixed venous blood oxygen saturation. Further, the blood lactate changes were paralleled by the pyruvate concentrations without an increase in excess lactate. He therefore concludes that lactate production is not controlled exclusively by the adequacy of cellular oxygenation but is also under the significant influence of pH, blood glucose levels and probably other stimuli yet unknown.[7]

In a series of reports relating to pyruvate and lactate during anaerobic metabolism[8,12] Huckabee has found that exercise with subsequent oxygen debt formation, and inhalation of low oxygen gases will produce calculated "excess lactate" concentrations which correspond well with the magnitude of oxygen debt developed.[8,9]

In-vitro experiments[13] suggest that lactate moves freely and passively across a permeable membrane according to the considerations of the Donnan equilibrium, while the pyruvate gradient is a result of cellular metabolic activity plus passive diffusion.

This is important in the interpretation of blood levels of pyruvate as being representative of tissue pyruvate concentration in metabolic studies. Furthermore, delay in the denaturation of blood causes much lower pyruvate and somewhat higher lactate concentrations, with much higher ratios of lactate to pyruvate than appear to exist in the body.[13] Because of differences in pH, pCO_2 and pO_2 and rates of flow between arterial and venous blood, it must be stressed that when knowledge of the total body aerobic-anaerobic state is being sought, only arterial blood samples are satisfactory.[2,7] Using a technique involving an indwelling needle in the brachial artery with collection of the blood samples in ice-cold 10% trichloracetic acid in 0.5 N HCl for rapid denaturation, Huckabee obtained the following results for basal conditions in the arterial blood of 69 normal human subjects:[7]

Lactate, 0.618 mM/L ($\delta = 0.077$)
Pyruvate, 0.142 mM/L ($\delta = 0.026$)
Lactate/Pyruvate ratio, 4.24 ($\delta = 0.44$)

Lactic Dehydrogenase

In regard to the rate of reaction of equation 1, it can be assumed, because of the distribution of the enzyme lactic dehydrogenase in all the tissues of the body, that this enzyme is present in excess and is not a normally limiting factor in the rate or direction of this reaction.[14,15] Bonting has found that the enzyme lactic dehydrogenase is almost exclusively located in the extramichrosomal extramitochondrial nonparticulate cell cytoplasm. This suggests the necessity of lactic acid being oxidized to pyruvic acid in the extramitochondrial cytoplasm prior to entering the glycolytic Krebs cycle in the mitochondria.[14]

Lactic dehydrogenase is a heterogenous protein molecule which exists as a tetramer* composed of four subunits of two parent molecules.[16] It has been shown that these two parent molecules which may be termed H (heart) and M (muscle), for the organs in which they are the predominant forms, have different electrophoretic, antigenic, amino acid and metabolic properties. The active enzyme may then be a tetramer of one of five possible combinations:

$$H_4, \quad H_3M, \quad H_2M_2, \quad HM_3, \quad M_4$$

Metabolically, these different forms of lactic dehydrogenase differ primarily in the degree to which they are inhibited by pyruvate. The type H_4, which is predominantly present in the heart, is maximally active at low concentrations of pyruvate, while being strongly inhibited if excess pyruvate is present. The M form, however, remains active at relatively high pyruvate concentrations. Functionally they are related to the requirements of their basic tissues. Cardiac muscle, which requires large amounts of a steady energy source, is benefited by an enzyme which functions best in the oxidative, aerobic cycle with complete oxidation of pyruvate to H_2O and CO_2 in the mitochondria, i.e., the free energy yield of the total oxidation of glucose is 686,000 cal per mole, while only about 8% of this or 56,000 cal per mole is available if the dissimilation of glucose proceeds only as far as lactic acid.[17]

In skeletal muscle, which may require the sudden, sporadic release of large amounts of energy in a relative insufficiency of oxygen, the enzyme M_4 which will function in the presence of large amounts of pyruvate provides a source of energy in a state of relative anaerobiosis. The lactate thus formed then enters the blood and is metabolized elsewhere. Experimentally, the ratios of M and H units of lactic dehydrogenase have been found to change in response to a variety of stimuli, including exposure to high or low oxygen concentrations, denervation and cell maturation.[16]

Biologically, the various zones of the kidney represent an example of graduated oxygen tensions in which the presence of lactic dehydrogenase subunits may be studied. Because of the counter-current pattern of circulation the papillae and medullary portions are relatively anoxic with reference to the cortex.[18] Analysis of lactic dehydrogenase concentrations in the various zones of rat kidneys reveals the following distribution of H subunits:[16]

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*See Test Your Word Score Page 672.

Zone	% of H Subunits
Papilla	9
Medulla	44
Cortex	98

Diphosphonucleotide-$DPNH_2$

The final major determinant in the rate and direction of equilibrium at equation 1 is the ratio of reduced to oxidized diphosphonucleotide in the non-particulate, extra mitochondrial cell sap. The significance of cell oxygenation and the adequacy of the respiratory pathway in the production of oxidized, active diphosphonucleotide have been discussed in detail elsewhere[19] in literature considering intracellcular hydrogen transport mechanisms. The importance of the redox potential of the cell as reflected by the ratios $DPNH_2$/diphosphonucleotide in the production of varying ratios of pyruvate and lactate is discussed by Huckabee[7,12] and previously mentioned in this paper.

Clearly then, any agent interfering with cellular respiration or hydrogen transfer within the cell will produce an altered redox potential, an accumulation of $DPNH_2$ and a consequent rise in total lactic acid. Furthermore, any reaction in the oxidation cycle which is catalyzed by a diphosphonucleotide dependent system of enzymes may produce, in the presence of excess substrate, an excess of $DPNH_2$ which in turn will drive our steady state equilibrium to the right, with consequent production of lactic acid.

Ungar, Psychoyos and Hall have shown[19] that phenethylbiquanide (DBI) when added to tissue and mitochondrial preparations in the concentration range $10^{-4}M$ will inhibit directly the diphosphonucleotide/dependent reactions of the Krebs cycle, i.e., the oxidation of citrate, keto-glutarate, fumarate, oxalacetate and pyruvate.

Phenethylbiquanide was also shown to inhibit oxidative phosphorylation in mitochondrial preparations. The addition of agents which uncouple oxidation from phosphorylation, such as 2, 4 dinitrophenol, dicumerol and salicylate, tended to reverse this inhibition. Experimentally, the addition of diphosphonucleotide and vitamins also reverses the effects of phenethylbiquanide on the tricarboxylic acid cycle. Ungar et al. interpret this as being caused by competition between diphosphonucleotide and phenethylbiquanide at some unknown enzymatic site. The inhibition of cellular respiration has been described[19] for the following drugs also:

P—aminophenol
Barbiturates
Diethel stilbesterol
Sulfonamides
Salicylates
Antabuse
Antihistamines
Adrenergic blocking agents
Chlorpromazine

Clinical Considerations

Definition

Lactic acidosis may be defined chemically as a metabolic acidosis characterized by a *reduced arterial pH* and the presence of *elevated levels* of *lactate* in the *extracellular fluids.*[4,20]

By definition then, we exclude the more common form of acidosis due to diabetes, uremia or ingestion of acidifying compounds. Likewise, we exclude the pronounced respiratory or metabolic alkalosis associated with elevated lactate concentrations in the absence of a reduced pH.[4,7]

Clinical Syndrome

Huckabee describes his nine patients as follows:

> "The first sign of lactic acidosis was usually *hypernea* with more or less marked *tachypnea*, and occasionally slight *cyanosis*. The patients usually also complained of *weakness, fatigue* and moderate to marked *dyspnea* in the early stages. The clinical syndrome progressed to *stupor* and finally to death."[5, p. 842]

Clinically, patients with lactic acidosis may be separated into two major groups. The metabolic acidosis associated with disease states significantly decreasing tissue oxygenation and consequently *increasing anaerobic metabolism*, OR conditions *inhibiting lactate utilization* may be considered *secondary lactic acidosis*. A second group consists of those patients in whom no satisfactory explanation can be given either in clinical or laboratory terms for their marked lacticacidemia. This is the same as Huckabee's group 2B in which all nine patients were acidotic and died, and it may be termed *idiopathic* lactic acidosis.[4,5,20]

Differential Diagnosis

Both laboratory studies and the appropriate history are extremely valuable in making the diagnosis in the presence of a severe metabolic acidosis of unexplained etiology.

Routine laboratory studies will show: (1) marked decrease in serum carbon-dioxide content, (2) low pH and (3) a large increase in the concentration of unmeasured anions, i.e., the "anion gap."

However, the presence of a marked anion gap does not in itself indicate lactic acidosis, since a variety of other disorders including diabetic ketoacidosis, salicylate and methyl alcohol poisoning, and azotemic renal failure will produce a metabolic acidosis characterized by the accumulation of anions other than chloride in the extracellular fluid.[21]

Also, the presence of an anion gap serves to exclude those metabolic disorders associated with a concomitant rise in chloride equal to the reduction in serum bicarbonate, including diarrhea, ammonium chloride intoxication and some forms of renal tubular disease.[21]

Causes of Lactic Acidosis

Spontaneous or idiopathic lactic acidosis by definition is the presence of "excess lactate" in the absence of known hypoxia, circulatory insufficiency or exogenous toxins. Metabolically this is meaningless, since the production of excess lactate is the result of anaerobic glycolysis. Clinically, to implicate hypoxia as a cause, we must postulate that normal blood pressures do not reflect the adequacy of tissue perfusion. Huckabee[5] has shown experimentally that lactic acidosis appears in dogs whose blood volumes have been reduced by slow hemorrhage, prior to a measurable change in circulation. Huckabee has also induced pericardial tamponade in dogs by the injection of plasma into the pericardial sac, and found a marked rise in excess lactate in the absence of any measurable change in cardiac output or blood pressure[5].

The possibility of some basic defect in one of the enzyme systems elsewhere in the Krebs cycle, such as the cytochrome oxidase system[20] or lactic dehydrogenase,[16] has been postulated.

The literature contains a number of case reports of *spontaneous lactic* acidosis.[21,22,23] In the references noted, one patient with tuberculosis who was operated on for pleural decortication and an extra-pleural-parietal fistula, at autopsy was found to have a diffuse perilobular hepatic necrosis.[22] Since the liver has been found[11,20] to play an important role in the metabolism of lactic acid, this case is suspect as an example of "spontaneous lactic acidosis." Likewise, for a variety of other reasons, the other cases are also suspect.

Secondary lactic acidosis has been found to be a sequela of a wide variety of other disease states. As early as 1925 Clausen, in his discussion of anhydramic acidosis (acute dehydration secondary to diarrhea and emesis), found a marked fall in bicarbonate and a concomitant rise in lactic acid, presumably secondary to circulatory insufficiency.[3] Peretz et al.[24] studied the metabolic acidosis of hypotensive shock in 25 patients and found that blood lactate was elevated ($>$ 1.3 mEq./L) in 24 of 25 patients and that there was good correlation between the rise in blood lactate, the fall in serum bicarbonate, and blood pH in early shock. Correction of the acidosis did not influence blood lactate levels significantly unless the circulation was improved concurrently.

Thus, in one instance a pH of 6.9 was corrected over two hours to 7.4 by administration of 500 mEq. of sodium bicarbonate intravenously. During this time the lactate rose from 132 mg./100 ml. to 148 mg./100 ml. This patient did not recover. It appeared that a decrease in blood lactate could be accomplished only with improved tissue perfusion, and in two instances this took place even in the presence of sustained hypotension after the administration of a sympatholytic agent, phenoxybenzamine (Dibenzyline.)[24]

Reynolds, Sherlock et al.,[25] studying the effect of hexamethonium bromide on the splanchnic system, found no significant alteration in splanchnic oxygen consumption, hepatic glucose output, and arterial and lactic acid concentrations in the presence of a "mean" blood pressure fall from 110 mm. Hg. to 80 mm. Hg.[25]

Paraldehyde intoxication has been found to induce a metabolic acidosis[26] which is not well understood. It may be related to the toxic effect of paraldehyde or its decomposition products, acetic acid and all acetaldehyde upon intermediary metabolism enzyme systems.

Eichenholz et al. have studied salicylate-induced metabolic acidosis in experimental dogs[27] and found that the rise in blood lactate and pyruvate levels accounted for most of the bicarbonate deficit present. Furthermore, the rise in lactate and pyruvate was preceded by a reduction in the pCO_2 secondary to the early respiratory alkalosis. Use of four percent CO_2 in the respired air to prevent respiratory alkalosis inhibited the occurrence of metabolic acidosis. Experimentally, the injection of minute quantities of sodium salicylate into the suboccipital cistern of a lightly anesthetized, spontaneously breathing dog produced a respiratory alkalosis with hyperventilation, decreased pCO_2 and a rise in lactate and pyruvate levels. There was no detectable salicylate in the animal's blood.

Acute leukemia associated with severe metabolic acidosis produced elevated lactic acid levels in 13 patients. In three of four patients, lactic acidosis diminished concurrently with a favorable response to antileukemic therapy. In-vitro lactic acid production was found to be low in the presence of normal oxygen tension but increased eight to twelve-fold with hypoxia.

Field et al. postulated on the basis of calculations utilizing the maximum in-vitro rate, that large aggregates of leukemia cells crowded into organs and, metabolizing anaerobically, could be the source of enough lactic acid to produce clinical lactic acidosis.[29] Lactic acidosis has also occurred in conjunction with a rare case of Reed-Sternberg cell leukemia. This relented following cytotoxic therapy.[30]

Familial infantile lactic acidosis in two siblings has been reported.[31] Each had a chronic metabolic acidosis which decreased in severity with increased age and both are mentally retarded. The basic cellular defect remains unknown.

Lactic acidosis with a necrotizing encephalopathy has been described in two other siblings in England. Both had identical symptoms of hypernea, progressive ataxia, mental deterioration and convulsions. At autopsy each showed degenerative changes of the central nervous system. One brother, who was investigated biochemically, was found to have a severe lactic acidosis. In two periods, when he was *not* hypernic, plasma lactate levels were found to be 30.5 and 38.7 mg. % (normal 6-18 mg. %). There was no "excess lactate" present.

Lactic acidosis of some severity has also been associated with glycogen storage disease.[33,34,35] The pathophysiology here remains obscure.

Daughaday et al.[36] have reported three cases of nonketotic acidosis in diabetic patients *not* receiving the oral hypoglycemic agent, phenformin.[36] Elevated blood lactate levels were present, but there was no detectable hypoxia. The etiology of this acidosis remains obscure.

Lactic acidosis and death, after the treatment of obesity by fasting, in a mild diabetic receiving no hypoglycemic agent has been reported.[37]

The literature contains many documented cases of lactic acidosis occurring in diabetics on phenethylbiquanide.[38,44] Although the exact relationship remains to be elucidated, the frequent association of phenethylbiquanide therapy and lactic acidosis cannot be ignored. Caution is recommended in the use of phenethylbiquanide in the treatment of diabetics when renal function has been impaired by acute or chronic disease.[38]

Therapy

The treatment of lactic acidosis is discussed at length by Huckabee,[5] Field,[28] Waters et al.,[21] and Tranquada.[20]

Two principles of treatment seem to be generally accepted:

(1) Vigorous correction of any possible cause of cellular hypoxia.

(2) Correction of the acidosis to near normal ranges with bicarbonate, i.e., maintenance of pH above 7.30, since in theory, some degree of acidosis may aid in the metabolism of lactate acid by driving our steady state equation to the left.

The use of lactate to correct the acidosis is not recommended.[28,45] In the physiologic range of pH, lactic acid is 99% ionized and unable to produce any direct buffering effect. The theoretical buffering effect of lactate is a product of lactate metabolism and concomitant hydrogen ion utilization. In the presence of excess lactate, as occurs in lacticacidosis, the infusion of *more* lactate presents an unnecessary osmotic load while remaining unavailable as a buffer.

Field[45] and Tranquada[46] have together treated a total of nine patients with methylene blue: a redox dye which can serve as an electron accepter for a number of physiologic oxidation reduction reactions. In Tranquada's series of five patients, methylene blue effected a significant reduction in blood lactate concentration of all five, when given doses in the range of 1.5 to 5.0 mg. per kg. However, only one of his patients survived.

Field treated four patients with from 4.3 to 12.5 mg./kg. of dye without apparent effect on blood lactate concentration and L/P ratios in three. There was an equivocal effect in the fourth patient.

It is felt that the most probable site of action of the dye, in relation to lactic acid production, is the direct or indirect oxidation of DPNH which would result directly in an increased conversion of lactate to pyruvate by driving our equilibrium equation to the left.[46]

Two organic hydrogen ion accepters, Tris (2-amino-2 hydroxy methyl-l, 3-propanediol[47]) and THAM (Tris-hydroxymethl aninomethane)[48] have been used in the treatment of lactic acidosis. Both would seem to provide a theoretical advantage in not being metabolized to CO_2 and consequently requiring respiratory exchange in excretion.

Tris buffer was used in the treatment of lactic acidosis following prolonged, cardiopulmonary bypass for repair of intracardiac defects in 20 patients.[47] The use of larger quantities of buffer (150 mg. per kg. body weight) produced rapid and sustained rises in arterial pH, plasma CO_2 and CO_2 combining power in 13 patients. In lesser doses, the response was minimal or transient.

The experience with hemodialysis in one case reported by Ewry[49] was encouraging. However, Tranquada et al.[20] had equivocal results using peritoneal dialysis with a lactate containing dialysate in three cases. The results were not interpretable in one case where they replaced lactate with acetate.

Finally, dextran has been suggested as an adjunct to therapy in an effort to increase tissue perfusion with blood.[28]

Practical Summary

Diagnosis: Clinical

1. Be suspicious—To make this diagnosis, *Lactic Acidosis* must be in your *differential diagnosis.*
2. Non-specific clinical picture of a metabolic acidosis includes:
   a. Tachypnea
   b. Hypernea
   c. Lethargy
   d. Malaise
   e. Dyspnea
   f. Stupor
   g. Cyanosis
3. Think of Lactic Acidosis particularly:
   a. In the presence of any basic underlying disease causing tissue hypoxia.
      (1) Severe congestive heart failure
      (2) Severe chronic lung disease
      (3) Shock
   b. In patients on oxidative enzyme toxins who have borderline renal

function, these drugs should be stopped immediately:
- (1) P-aminophenol
- (2) Barbiturates
- (3) Diethyl stilbesterol
- (4) Sulfanamides
- (5) Salicylates
- (6) Antabuse
- (7) Antihistamines
- (8) Adrenergic blocking agents
- (9) Chlorpromazine
- (10) DBI, Phenphormin

Diagnosis: Laboratory

1. Use arterial blood only
2. The following suggest a metabolic acidosis with lacticacidemia
    a. Acid pH
    b. Low serum HCO_3
    c. Presence of an "*anion gap*"
    Calculate anion gap from serum electrolyte values as follows:
    Anion gap (AG) $= (Na^+ + K^+) - ((Cl^-) + HCO_3^- + 12)$
    If AG = 10 mEq/L or more consider lactic acidosis.
    Anion gap may also be present in other metabolic acidosis, i.e.,
    (a) Diabetic ketoacidosis
    (b) Salicylate } intoxication
    (c) Methyl alcohol } intoxication
    (d) Azotemic renal failure
3. If above criteria suggest lactic acidosis, determine blood lactate and pyruvate levels.

Therapy

1. Treat any cause of hypoxia *vigorously!!*
    a. Give O_2 10/L/min with humidity
    b. Give digitalis if in heart failure
    c. Maintain adequate pulmonary ventilation—intubate and use respirator as needed
    d. Use vasopressors *sparingly* in shock—intense, peripheral vasoconstriction will enhance tissue hypoxia and increase lactic acid production
    Use (1) Fluid replacement: blood, plasma, albumin
    (2) Steroids
    (3) Isuprel
    as indicated, rather than Aramine or Levophed if possible.
2. Correct acidosis to pH 7.30 in first two hours
    a. Use HCO_3^-, not lactate-containing solutions. This may require *massive* doses of HCO_3^-, to 500 mEq. or more.
    Give *INTRAVENOUSLY*.
3. Follow electrolytes, arterial pH, PO_2, PCO_2, and anion gap at 2-4 hour intervals during the acute phase.
4. The judicious use of:
    a. Dextran
    b. Hexamethanium bromide
    To increase tissue perfusion may be of value in selected cases, but are unproven adjuncts at this time.

Appendix

The lactic dehydrogenase system may be depicted by:

1. $C_3H_4O_3 + DPNHH^+ \rightleftarrows C_3H_5O_3 + DPN$ or by the mass action form.
2. $[Pyruvate] \times [DPNHH^+] = K\ [Lactate] \times [DPN]$ which may be rearranged to show the two physiologic factors affecting lactate concentration at any time t_o:
3. $$[Lactate]_o = [Pyruvate]_o \times K \frac{[DPNH^+H]_o}{[DPN]_o}$$

   The difference in lactate between t_o and any other time t_n provided there is no hypoxia, will be:
4. $$[Lactate]_n - [Lactate]_o = [Pyruvate]_n - [Pyruvate]_o \times K \frac{[DPNH_2]_o}{[DPN]}$$

   Substituting from equation (3) the value obtained by solving for $K \dfrac{[DPNH_2]_o}{[DPN]_o}$
5. $$[Lactate]_n - [Lactate]_o = [Pyruvate]_n - [Pyruvate]_o \times \frac{[Lactate]_o}{[Pyruvate]_o}$$

   The difference between the value $L_n - L_o$ predicted from equation 5 on the assumption that no true hypoxia occurred within the cells and the value of $L_n = L_o$ actually observed to occur is the "excess lactate:"
6. $$XL = \triangle L - \triangle L$$

   and in terms of measurable quantities (all concentrations):
7. $$XL = (L_n - L_o) - (P_n - P_o)\ (L_o/P_o)$$

A sample calculation gives the following result:

Basal blood lactate = 0.550 mM per L.
Basal blood pyruvate = 0.135 mM per L.
Experimental lactate value = 2.680 mM per L.
Experimental pyruvate value = 0.409 mM per L.

$$XL = (2.680 - 5.550) - (0.409 - 0.135)\frac{(0.550)}{(0.135)} = 2.130 - 1.115$$

$$XY = 1.015 \text{ mM per L.}$$

References may be secured from the Grand Rounds Editor.

The Patient in the Hospital

These sick people are isolated "specimens." They are segregated from their environment, removed from the circumstances under which they became ill, separated from their families, stripped even of their clothes; all of which is done to create a proper atmosphere for diagnostic study and careful management on the physician's part, free from outside distractions. It may be trite to point out that these "outside distractions" are the very things which the modern doctor, or the student interested in preventive medicine, needs to study also. For if one is to handle patients adequately, it is necessary to bring clinical judgment to bear not only on the patient, but also on the circumstances under which his illness arose.*

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*J. R. Paul in Richard Magraw: Ferment in Medicine, 1966.

Prophylactic Use of Lincomycin in Oral Surgery

PREVIOUSLY, MEMBERS of our group have described some of our experiences with different antibiotics in the attempted prevention of bacterial invasion of the blood after oral surgical procedures.[1-6] Lincomycin hydrochloric monohydrate was selected for a continuation of these studies. The spectrum of antibacterial activity of lincomycin includes *Staphylococcus aureus*, β-hemolytic streptococcus, and *Streptomyces viridans*. It is not active against most trains of entercococci, such as *Streptoccus faecalis,* or against *Neisseria* organisms or gram-negative bacilli.[7,8] Reasons for studying lincomycin included the possible occurrence of postoperative bacterial endocarditis due to penicillin-resistant streptococci,[9-10] the inability of certain patients to tolerate alternative drugs, and the antistaphylococcal property of the antibiotic. The purpose of this project was to investigate the effectiveness of lincomycin, compared to that of drugs previously studied, under the conditions outlined.

Methods and Materials

The patients selected were those undergoing an oral surgical procedure. These procedures consisted of multiple extractions, followed by alveoloplasty because of caries, periodontal disease, or both, and odontectomy of impacted third molars. Lincomycin hydrochloride monohydrate* was administered in capsule form in four successive doses of 500 mg, beginning 18 hours prior to operation. The patients were requested not to take food within a two-hour period before and after taking the medication. Blood for culture was drawn in the operating room immediately after the operation and again approximately 18 hours later. Fifty patients were included in this study; none of these had urinary obstruction or evidence of renal disease, preexisting systemic infection, or cardiovascular defects that would make them susceptible to the development of endocarditis or endarteritis.

Results

Three of the 50 patients had positive cultures from the blood taken immediately after the oral surgical procedure. In two, *Streptococcus mitis* was cultured and, in the third, the organisms were *Neisseria catarrhalis* and *S. mitis*. However, cultures of the blood taken from all 50 patients 18 hours after the operation were negative (Table).

Comment

It is noteworthy that the blood cultures obtained from patients in this study did not reveal staphylococci. In contradistinction to this finding, blood cultures obtained from 6% of our patients receiving phenoxymethyl penicillin[3] and 3.7% of those receiving cloxacillin[4] grew staphylococcal organisms. In the studies of erythromycin[5] and nafcillin,[6] none of the blood cultures revealed staphylococci.

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*Supplied as Linocin, courtesy of the Upjohn Company, Kalamazoo, Mich.

Six per cent of the blood cultures obtained after operation from patients in this study grew *S. mitis,* which compares favorably to the 15% of blood cultures obtained from patients receiving cloxacillin[4] and the 21% of those obtained from patients receiving nafcillin[6] that grew streptococcal organisms. However, it should be stressed that those patients receiving optimal amounts of phenoxymethyl penicillin[1,3] or erythromycin[5] had consistently negative blood cultures for *S. mitis.* Because postoperative invasion of the blood by *S. mitis* is especially feared as a mechanism in the genesis of bacterial endocarditis, our studies to date indicate that phenoxymethyl penicillin and erythromycin are superior to the other drugs studied for prophylaxis prior to oral surgery.

Currently, we are studying ampicillin, which theoretically should produce antistreptococcal effects similar to those achieved on administration of phenoxymethyl penicillin and might in addition decrease the incidence of postoperative invasion of the blood by gram-negative bacilli. In our studies employing phenoxymethyl penicillin for prophylaxis prior to oral surgery, we have noted such gram-negative bacillary invasion of the blood.[1,3]

Ultimately, we hope to restudy both lincomycin and nafcillin when these drugs are given for a longer period before operation, in an attempt to determine the total dosage required to achieve an optimal antistreptococcal effect. Similarly, we hope either to restudy cloxacillin or to study dicloxacillin: a newer isoxazolyl penicillin[11] that provides even higher levels in the blood than does cloxacillin.

Summary

Fifty patients were studied, each of whom received four doses of 500 mg of lincomycin beginning 18 hours before oral surgery. In three (6%) of the patients, cultures of the blood taken immediately after surgery grew *Streptococcus mitis.* One of these three cultures also grew *Neisseria catarrhalis.* None of the cultures revealed staphylococcal organisms. Although lincomycin compares favorably with erythromycin and nafcillin in preventing invasion of the blood by staphylococcal organisms, it is not as effective as phenoxymethyl penicillin or erythromycin in controlling such invasion by *S. mitis.*

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*Mayo Clinic and Mayo Foundation: Section of Dentistry and Oral Surgery.
†Mayo Clinic and Mayo Foundation: Section of Medicine.

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It is a great misfortune neither to have enough wit to talk well nor enough judgment to be silent.—La Bruyere

See next page for prescribing informa

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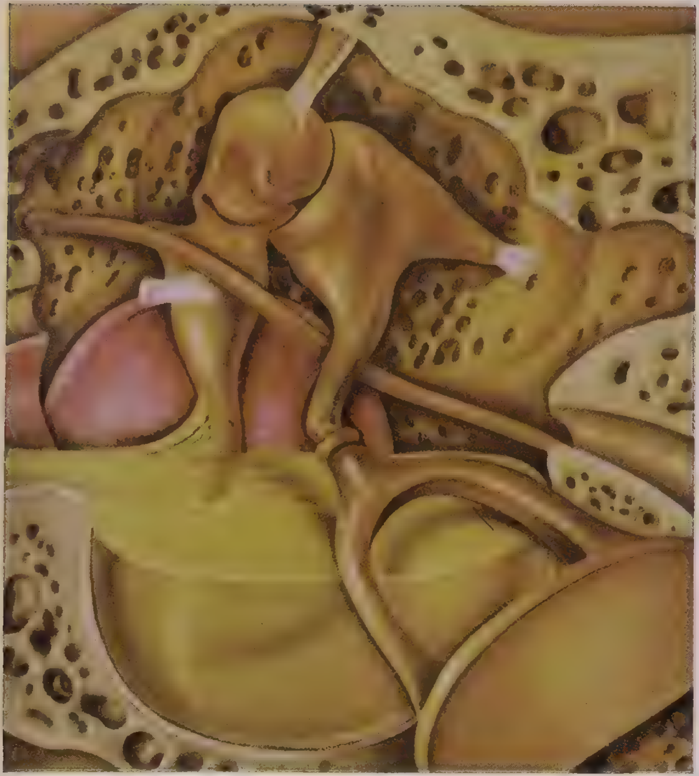

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Precautions: Overgrowth of nonsusceptible organisms may occur. Constant observation is essential. If new infections appear, appropriate measures should be taken. In infants, increased intracranial pressure with bulging fontanels has been observed. All signs and symptoms have disappeared rapidly upon cessation of treatment.
Side Effects: Gastrointestinal system—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. Skin—maculopapular and erythematous rashes; a rare case of exfoliative dermatitis has been reported. Photosensitivity, onycholysis and discoloration of the nails (rare). Kidney—rise in BUN, apparently dose-related. Transient increase in urinary output, sometimes accompanied by thirst (rare). Hypersensitivity reactions—urticaria, angioneurotic edema, anaphylaxis. Teeth—dental staining (yellow-brown) in children of mothers given this drug during the latter half of pregnancy, and in children given the drug during the neonatal period, infancy and early childhood. Enamel hypoplasia has been seen in a few children. If adverse reaction or idiosyncrasy occurs, discontinue medication and institute appropriate therapy. Demethylchlortetracycline may form a stable calcium complex in any bone-forming tissue with no serious harmful effects reported thus far in humans.
Average Adult Daily Dosage: 150 mg q.i.d. or 300 mg b.i.d. Should be given 1 hour before or 2 hours after meals, since absorption is impaired by the concomitant administration of high calcium content drugs, foods and some dairy products. Treatment of streptococcal infections should continue for 10 days, even though symptoms have subsided.

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Review

Steroid Diabetes

THE DIABETOGENIC action of several hormones has long been recognized. As far back as 1901 parenteral administration of the active principle of the adrenal medulla was found to produce diabetes.[1] Later it was shown that anterior pituitary extract can also produce diabetes.[2,3] Adrenalectomy was found to ameliorate experimental diabetes in cats,[4] and subsequently the role of the adrenal cortex in carbohydrate metabolism in man was extensively studied.[5-7]

The purpose of this article is to review briefly the effects of "carbohydrate-active" adrenal steroids (glucocorticoids) as related to carbohydrate metabolism. The term "steroid diabetes" is used to designate the development of decreased tolerance for carbohydrate in the presence of excessive glucocorticoid of either endogenous or exogenous origin.[7,8]

Mechanism of Steroid Diabetes

Accumulated evidence indicates that adrenocorticosteroids are powerful hormonal agents which are capable of influencing many tissues of the body. In particular, glucocorticoids are intimately involved in the metabolism of carbohydrate. The impaired carbohydrate tolerance in steroid diabetes involves both overproduction and underutilization of glucose.

Glucose Production

Adrenal steroids stimulate gluconeogenesis from noncarbohydrate sources, mainly through a catabolic action on protein.[9,10] Liver is the principal site of gluconeogenesis. Gluconeogenesis results in increased glycogen synthesis and storage in both liver and muscle. While glucocorticoids increase hepatic glucose production, insulin antagonizes this by decreasing gluconeogenesis. Evidence for gluconeogenesis following glucocorticoid administration includes: (1) increased extra-hepatic protein catabolism, increased plasma amino acids and widespread protein depletion,[11] (2) increased hepatic uptake of plasma amino acids,[12] and (3) increased rate of transamination and deamination in the liver.[13]

It has been suggested that an increase in the activities of certain specific hepatic phosphatases following cortisone administration may augment glucose production.[14,15] However, this is felt to reflect an increase in gluconeogenesis rather than a primary process for glucose formation.[16]

Glucose Utilization

Loss of carbohydrate tolerance is probably not fully explained by gluconeogenesis from protein.[17] An additional mechanism might be conversion of fat to glucose. Glucocorticoids stimulate the release of free fatty acids from adipose tissue.[18] Unlike epinephrine-induced lipolysis,[19] this process is not associated with oxidation of glucose. However, since significant conversion of fat to glucose does not occur, one must assume that utilization of carbohydrate by peripheral tissues has been impaired.[5] Since insulin is the primary hormone involved in the regulation of glucose utilization, this impairment is probably due to direct antagonism of glucocorticoids to insulin at a cellular level.

Regulation of Phosphorylation

Glucocorticoids are not involved in the regulation of glucose phosphorylation by liver.[20] Insulin stimulates and cortisol decreases glucose uptake by adipose tissue in vitro.[21] Furthermore, cortisol diminishes lipogenic activity in both hepatic and adipose tissues.[22] The effect of glucocorticoids on muscle is profound. In normal muscle, adrenal hormones seem to be involved in the regulation of both glucose phosphorylation and cell permeability. In the presence of insulin, phosphorylation, rather than penetration, becomes rate-limiting.[23] It has been shown that adrenal cortical extract can modify the hexokinase reaction by intensifying the inhibitory effect of anterior pituitary extract upon the action of insulin.[24] In muscle the hormones of the adrenal cortex decrease the conversion of carbohydrate and acetate to fat, favor the formation of lactate, and diminish the oxidation of pyruvate. Lactic acid is then oxidized rather than being repolymerized to glycogen,[25-27] which may explain in part the elevated plasma lactate and pyruvate in hyperadrenocorticism.

The effects of both glucocorticoids and insulin on the metabolism of liver, muscle and adipose tissue are summarized in the table.

TABLE*

Effects of Insulin and Glucocorticoids Upon Tissue Metabolism

PARAMETER	HORMONE	LIVER	MUSCLE	ADIPOSE
Glucose Utilization	Insulin	↑	↑	↑
	Corticoids	0	0	↓
Glucokinase Activity	Insulin	↑	0	?
	Corticoids	0	↓	?
Fatty Acid Synthesis	Insulin	↑	?	↑
	Corticoids	↓	?	0
Free Fatty Acid Release	Insulin	?	↓	↓
	Corticoids	?	?	↑
Protein Synthesis	Insulin	↑	↑	↑
	Corticoids	0	↓	↓

increased	↑
no effect	0
decreased	↓

*Modified from Ashmore, J.[20].

Characteristics of Steroid Diabetes

There is general agreement that endogenously and exogenously induced adrenal steroid diabetes are similar. Steroid diabetes has several features that distinguish it from pancreatic diabetes. It is usually mild and disappears with correction of the steroid excess upon which it depends.[7,28] Even in steroid diabetes of long standing the diabetic state may not be permanent.[28] There is a tendency toward insulin insensitivity, negative nitrogen balance, and elevated levels of blood pyruvate and lactate.[5,29] Blood sugar is rarely greatly elevated, and occasionally there may be renal glycosuria which has been attributed to decreased tubular reabsorption of glucose.[30,31] Ketosis is rare and glycosuria is likely to be absent during fasting.[5,29]

Administration of cortisone or physiologically related steroids, or of adrenocorticotropic hormone, to normal subjects may produce temporary hyperglycemia, glycosuria and decreased glucose tolerance.[32-34] It has been shown that impairment of glucose tolerance may be induced in many nondiabetics when large doses of glucocorticoids are used and that the degree of impairment depends upon the potency and dose of the drug used, the duration of administration and the recipient.[35-37] The variation in individual response to the cortisone-induced impairment of glucose tolerance can be used as a test to unmask the potential diabetic who has a normal carbohydrate tolerance on other tests.[38]

The development of diabetes in patients receiving adrenal steroids is a rare occurrence. A transitory diabetic state was noted in only a few of several hundred patients who received cortisone or corticotrophin.[39] In the great majority of normal people, after an initial decrease in carbohydrate utilization, tolerance returns to normal despite continuation of glucocorticoid administration. This has been interpreted as an attempt on the part of the beta cells to compensate for the decreased glucose utilization and increased glucose production (see above).[5]

Adrenal Cortex and Diabetes Mellitus

Whether adrenal cortical dysfunction plays a role in diabetes mellitus and its vascular complications in man has received much attention.[5,6,40,42] It has been suggested that increased adrenal cortical function exists in patients with diabetes mellitus.[43] Although decreased excretion of 17-ketosteroids was found in diabetics, there was no apparent correlation between the amount of 17-ketosteroids excretion and the severity of diabetes.[40] Several workers have reported great elevations in the urinary corticosteroids in patients with diabetic acidosis.[44,45] It is suggested that in the depancreatized rat the glucocorticoids produce ketosis by mobilizing fat to liver and by accelerating ketogenesis by the liver.[46] Thus important hormonal factors for ketosis are insulin deficiency and glucocorticoid excess. In the intact animal the glucocorticoid-induced hyperglycemia may stimulate insulin production, which in turn inhibits ketogenesis.[6]

In adrenal cortical hyperfunction of the type which produces Cushing's syndrome a diabetic glucose tolerance curve was present in 94 percent of cases, but frank diabetes was observed in only 14 percent.[47] Co-existence of Addison's disease and diabetes mellitus is much less frequent; only 113 cases were collected by 1965.[48] Since Addison's disease preceded diabetes in 71 cases, it is evident that adrenocortical insufficiency does not necessarily protect against subsequent development of diabetes mellitus. While the role of the adrenal gland in human diabetes has not been precisely defined, most investigators agree that there is little evidence to support adrenal cortical dysfunction among patients with diabetes mellitus.[29,42]

Summary

A brief review of the major effects of the adrenal steroids upon glucose metabolism is presented. Glucocorticoids of either endogenous or exogenous origin may result in an impairment of glucose tolerance (steroid diabetes). The characteristics of steroid diabetes are discussed. The possible relation

of the adrenal cortex to diabetes mellitus is also discussed.

Acknowledgement

The author is greatly indebted to Dr. R. G. Sprague for reviewing the manuscript and for helpful suggestions.

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12-48. May be secured from the author or the reprints.

Test Your Word Score

Waldeyer's ring—*lymphoid tissue formed by the lingual, pharyngeal and faucial tonsils* (page 576).

Thoracostomy—*cutting operation into the chest cavity* (page 589).

Efflux—*effluvium, noxious discharge.* (page 591).

Myopathy—*any disease of a muscle* (page 596).

Annuloplasty—*surgical formation of a ring* (page 609).

Trophic—*of or pertaining to nutrition* (page 632).

Hamartoma—*a tumor-like nodule of superfluous tissue* (page 639).

Herald—*forerunner or harbinger* (page 653).

Tetramer—*a four-sided entity* (page 657).

Abstracts, Briefs and Commentaries

COMPLICATIONS FOLLOWING RESUSCITATION

External cardiac massage was introduced in 1960. This method combined with artificial ventilation has been widely used and is occasionally accompanied by complications. Related to chest massage the most common complications are fractures of the ribs, fracture of the sternum, rupture of the liver, rupture of the spleen, bone-marrow emboli, hemothorax, pulmonary hemorrhage, hematoma or rupture of the heart, hemorrhage of the pancreas, and retroperitoneal hemorrhage.

Intracardiac injections may cause pneumothorax or hemopericardium. Improper artificial ventilation in the newborn may result in interstitial emphysema, pneumomediastinum, pneumothorax and/or pneumoperitoneum. From January 1964 to April 1967, 16 patients died from resuscitation efforts and have been autopsied at the Pathology Department at the Ulleral Hospital. Rib and sternum fractures were the most common findings following cardiac massage. All 16 cases are briefed here.

Case 1

An eight-hour-old infant received external cardiac massage and mouth-to-mouth/nose breathing by a doctor. Autopsy revealed prematurity and atelectatic lungs, a tear in the liver and blood in the peritoneal cavity.

Case 2

A 17-hour-old premature became cyanotic. External cardiac massage and mouth-to-mouth/nose breathing were done by a doctor for 10 minutes. Autopsy revealed mitral stenosis, atresia of the aorta, a tear in the liver and 20 ml. of blood in the peritoneal cavity.

Case 3

A 31-hour-old infant, born asphytic, was given external cardiac massage and mouth-to-mouth/nose breathing by a doctor. Autopsy revealed atelectatic lungs, hyaline membrane disease, rupture of the liver 6 cm. in length and blood in the peritoneal cavity.

Case 4

An 18-month-old infant developed gastroenteritis and became unresponsive. External cardiac massage and mouth-to-mouth breathing were performed by an ambulance attendant during transport. Autopsy revealed acute enteritis, cerebral edema, fatty infiltration of the liver, a rupture of the lesser curvature of the stomach (2 cm.), pneumoperitoneum and collapse of the lungs with tension pneumothorax.

Case 5

A 43-year-old man collapsed at home. In the hospital emergency room he received external cardiac massage and artificial respiration. Autopsy revealed multiple pulmonary emboli, thrombi in the periprostatic veins and a tear in the spleen 4 cm. long.

Case 6

A 46-year-old man collapsed on the street. In the emergency room he received cardiac massage and intratracheal intubation by a doctor. Autopsy revealed coronary disease, fractures of the third through the sixth ribs on the left side, fracture of the sternum, a tear 7 cm. long in the liver and 100 ml. of blood in the peritoneal cavity.

Case 7

A 57-year-old man collapsed at home. During transportation to the hospital external cardiac massage and mouth-to-mouth breathing were performed. In the hospital he was given cardiac massage and intratracheal intubation by a doctor. Autopsy revealed coronary occlusion, rupture of the liver (2 cm.) and 400 ml. of blood in the peritoneal cavity.

Case 8

A 62-year-old man with abdominal pain and shock was brought to the hospital. An abdominal aneurysm required surgery. On the first postoperative day he developed cardiac arrest, and external cardiac massage was performed by a doctor. Autopsy revealed intact transplant of the aorta, fracture of the fourth and fifth ribs on the right side, 700 ml. of blood in the peritoneal cavity, and a 7-cm. rupture of the liver.

Case 9

A 64-year-old man with chest pain collapsed at home. During transportation to the hospital an ambulance attendant performed external cardiac massage. Autopsy revealed coronary disease with old infarction, multiple fractures of the ribs, and a tear of the liver 4 cm. long.

Case 10

A 65-year-old man with chest pain entered the hospital. A diagnosis of myocardial infarction with collapse was treated by a doctor by external cardiac massage. Autopsy revealed coronary occlusion and rupture of the heart.

Case 11

A 68-year-old man was given external cardiac massage by an ambulance attendant. Autopsy showed myocardial infarction, multiple rib fractures, hemorrhagic patches in the lungs and hemorrhage around the portal vein.

Case 12

A 63-year-old woman was treated for fractures of the left ankle. Two weeks later she collapsed. House doctors performed external cardiac massage and intratracheal intubation with positive pressure for three hours. Autopsy showed a large pulmonary embolus, thrombosis of the femoral vein, fracture of the sternum, fracture of the right second and third ribs, and of the second through the sixth ribs on the left side, rupture of the spleen 4 cm. in length and 3000 ml. of blood in the peritoneal cavity.

Case 13

A 70-year-old woman entered the hospital with myocardial infarction and collapsed. External cardiac massage and mouth-to-mouth breathing were performed by a doctor. Autopsy showed coronary occlusion, myocardial infarction with rupture of the heart, a rupture of the liver (6 cm.), and tears 4 cm. in length in the mucosa of the lesser curvature of the stomach.

Case 14

A 71-year-old woman collapsed immediately on entering the hospital. External massage was rendered by a doctor. Autopsy showed myocardial infarction, fatty infiltration of the liver, with a tear 2 cm. in length, multiple deep ruptures, and 400 ml. of blood in the peritoneal cavity.

Case 15

A 78-year-old woman collapsed in the hospital emergency room. External cardiac massage and mouth-to-mouth breathing were employed by nurses. Autopsy showed coronary occlusion, myocardial infarction, multiple fractures of the ribs and 300 ml. of blood retroperitoneally.

Case 16

An 82-year-old woman collapsed soon after entering the hospital. External cardiac massage and intratracheal intubation with positive pressure were rendered by a doctor. During the artificial ventilation cervical emphysema was noted. Autopsy revealed severe coronary sclerosis, old myocardial infarctions, multiple fractures of the ribs, a rupture of the spleen (5 cm.) with

300 ml. of blood within the peritoneum, and severe pneumomediastinum.

Comments: Experiences reveal both the benefits and the hazards of resuscitation. The record states that of the 16 reported emergency cases eleven were treated by doctors, one by nurses and three by ambulance attendants.

Rib fractures may occur when pressure is applied to the side of the midline, and lacerations of the liver when pressure is applied over the tip of the sternum. Two cases that had rupture of the liver had fatty infiltration; three were in children because of the higher position of that organ. Mouth-to-mouth breathing frequently produces distention of the stomach, most often in children. "Most of the complications are probably due to unsatisfactory technique."

Discussion

The unhappy results disclosed in this article are shocking but rewarding. It takes honesty and courage to report such experiences. It proves without doubt the need of proper teaching of methods of resuscitation to all who may be required to give first aid. The services in the above reports were given by doctors, nurses and ambulance attendants and reveal the need of instructing persons who might happen to be required to act in an emergency. This article brings out the fact that even highly trained personnel can make mistakes that cause fractures of the chest wall and injury to thoracic and abdominal viscera.

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Moe, Narve: Department of Pathology, Ullevål Hospital, University of Oslo, Oslo, Norway: Complications following Resuscitation.

RATE OF FORMATION OF COMMON BILE DUCT STONES FROM NONABSORBABLE SILKWORM GUT

"A case is reported in which 10 days after choledocholithotomy and transduodenal sphincterectomy, silkworm ligatures, used to suture the cystic duct and a vein near the common bile duct wall, had passed into the common duct, and calcium bilirubinate had accumulated on their surface to form gallstones."

Fresh calculus formation after removal of the gallbladder, using nonabsorbable suture material, has been reported several times. From these previously reported cases, however, it is not clear how quickly nonabsorbable sutures placed outside the bile ducts pass into the ducts to form a nucleus for new stones.

This patient, a female 61 years of age, had been operated on for gallstones one year previously; a preoperative x-ray study had revealed dilated common duct and stones. At operation the common duct was opened, the stones were removed, and transduodenal sphincterectomy was performed. A bleeder near the common duct was ligated with silk; a stump of cystic duct left at previous surgery was removed and sutured with silk; and a t-tube was placed in the common duct.

The patient evidently did poorly, and six days later x-ray revealed inadequate filling of the right hepatic duct, poor exit through the common duct, and also stones. After 10 days, re-laparotomy was performed with choledocholithotomy, and a number of stones were removed.

Postoperative study of the stones revealed silk ligatures in two. Several factors (necrosis and infection) may contribute to loosen nonabsorbable sutures outside the duct, thus enabling them to find their way into the common duct. Suction inside the common duct towards the intestine, produced by duodenal tonus and peristalsis, is enough to produce this effect. (Sandblom et al. 1935; Watts and Dumpy 1966). Even sutures of nonabsorbable material within the abdominal wall have found their way into the common duct.

Note: In this article the time element between the first and the second operation with the reformation of stones was only 10 days.

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*Oppolzer 1965-Wein, Klein Waschf 8-128.

Lormi Teuro and Silvennoinen Ensio; Department of Surgery, University of Oulu, Oulun Laanensairaada, Oulu, Finland: Rate of Formation of Common Bile Duct Stones from Nonabsorbable Silkworm Gut.

Are Doctors Human?

The truth is that doctors *are* human; that they seem otherwise at times is purely the fault of us patients. Doctors know our deepest secrets not by some demoniac process of mental telepathy but because we insist on trotting the secrets out. We do this ostensibly to aid in treatment, actually to ease our guilty consciences or to show what rips we are or maybe just to keep the old tongue wagging.

Doctors are pampered, certainly, and yet how many of them go out of their way to attract an excess of esteem? Generally it comes to them against their will and for reasons so transparent that a two-year-old could see through them. So-and-So butters Dr. Smith to the skies at Mrs. Jones' bridge party, hoping to get a bit of free medical advice later on in the evening. Mr. Brown is also there buttering away at a great rate.

Closely connected with the pampering is the tendency to envelop doctors in an aura of infallibility. . . . Few doctors relish this role of infallibility. They know perfectly well that the real workers of miracles are the patients themselves, nine out of ten of whom meet the test of illness with astonishing heroism, persistence, patience, and self-discipline. Doctors set the stage by surgery or medicine or advice. The patient has to put the show over.

Every one of my sixteen docs has been ready and eager to admit that he is as apt to pull bloopers as any professional man or craft worker. The surgeon who yanked out my appendix frankly informed me next day that the appendix was not my trouble and that he was darned if he could find anybody who could tell him what *was* my trouble. Six months later I went through a diagnostician's clinic, garbed in a sheet like Gandhi and drinking gallons of barium. After two days of this, the head diagnostician announced his findings. "All I can discover," he said sheepishly, "is that you're allergic to turnips. To be honest with you, that doesn't mean a thing. Practically everybody I ever put through the clinic is allergic to turnips."

My present doctor has a favorite yarn about a convalescent in our hospital who hadn't seen his doctor in two years. When the doctor finally turned up, he said to the anxious convalescent, "Are you still here? Why, I meant to tell you two years back to get up and go home!"*

---

*Sprague, Marshall: The Business of Getting Well. 1943.

In the complex picture of moderate to severe anxiety...

there is a new reason for prescribing Mellaril (Thioridazine HCl)

effectiveness in mixed anxiety-depression

Long recognized for its usefulness in the treatment of moderate to severe anxiety, Mellaril is now also known to be effective against mixed anxiety-depression.

Often the symptoms of anxiety states are difficult to sort out—even with the most careful probing. The patient may manifest symptoms of agitation, restlessness, insomnia, somatic complaints. But what of the depression that may be mixed in the total picture? It is reassuring to know that Mellaril may be prescribed—with strong possibilities of success—when there is anxiety alone or a mixture of anxiety and depression.

Before prescribing or administering, see Sandoz literature for full product information, including adverse reactions reported with phenothiazines. The following is a brief precautionary statement.
Contraindications: Severe central nervous system depression, comatose states from any cause, hypertensive or hypotensive heart disease of extreme degree.
Warnings: Administer cautiously to patients who have previously exhibited a hypersensitivity reaction (e.g., blood dyscrasias, jaundice) to phenothiazines. Phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides. During pregnancy, administer only when necessary.
Precautions: There have been infrequent reports of leukopenia and/or agranulocytosis and convulsive seizures. In epileptic patients, anticonvulsant medication should also be maintained. Pigmentary retinopathy may be avoided by remaining within the recommended limits of dosage. Administer cautiously to patients participating in activities requiring complete mental alertness (e.g., driving). Orthostatic hypotension is more common in females than in males. Do not use epinephrine in treating drug-induced hypotension. Daily doses in excess of 300 mg. should be used only in severe neuropsychiatric conditions.
Adverse Reactions: *Central Nervous System*—Drowsiness, especially with large doses, early in treatment; infrequently, pseudoparkinsonism and other extrapyramidal symptoms; nocturnal confusion, hyperactivity, lethargy, psychotic reactions, restlessness, and headache. *Autonomic Nervous System*—Dryness of mouth, blurred vision, constipation, nausea, vomiting, diarrhea, nasal stuffiness, and pallor. *Endocrine System*—Galactorrhea, breast engorgement, amenorrhea, inhibition of ejaculation, and peripheral edema. *Skin*—Dermatitis and skin eruptions of the urticarial type, photosensitivity. *Cardiovascular System*—Changes in the terminal portion of the electrocardiogram have been observed in some patients receiving the phenothiazine tranquilizers, including Mellaril (thioridazine hydrochloride). While there is no evidence at present that these changes are in any way precursors of any significant disturbance of cardiac rhythm, several sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients previously showing electrocardiographic changes. The use of periodic electrocardiograms has been proposed but would appear to be of questionable value as a predictive device. *Other*—A single case described as parotid swelling.

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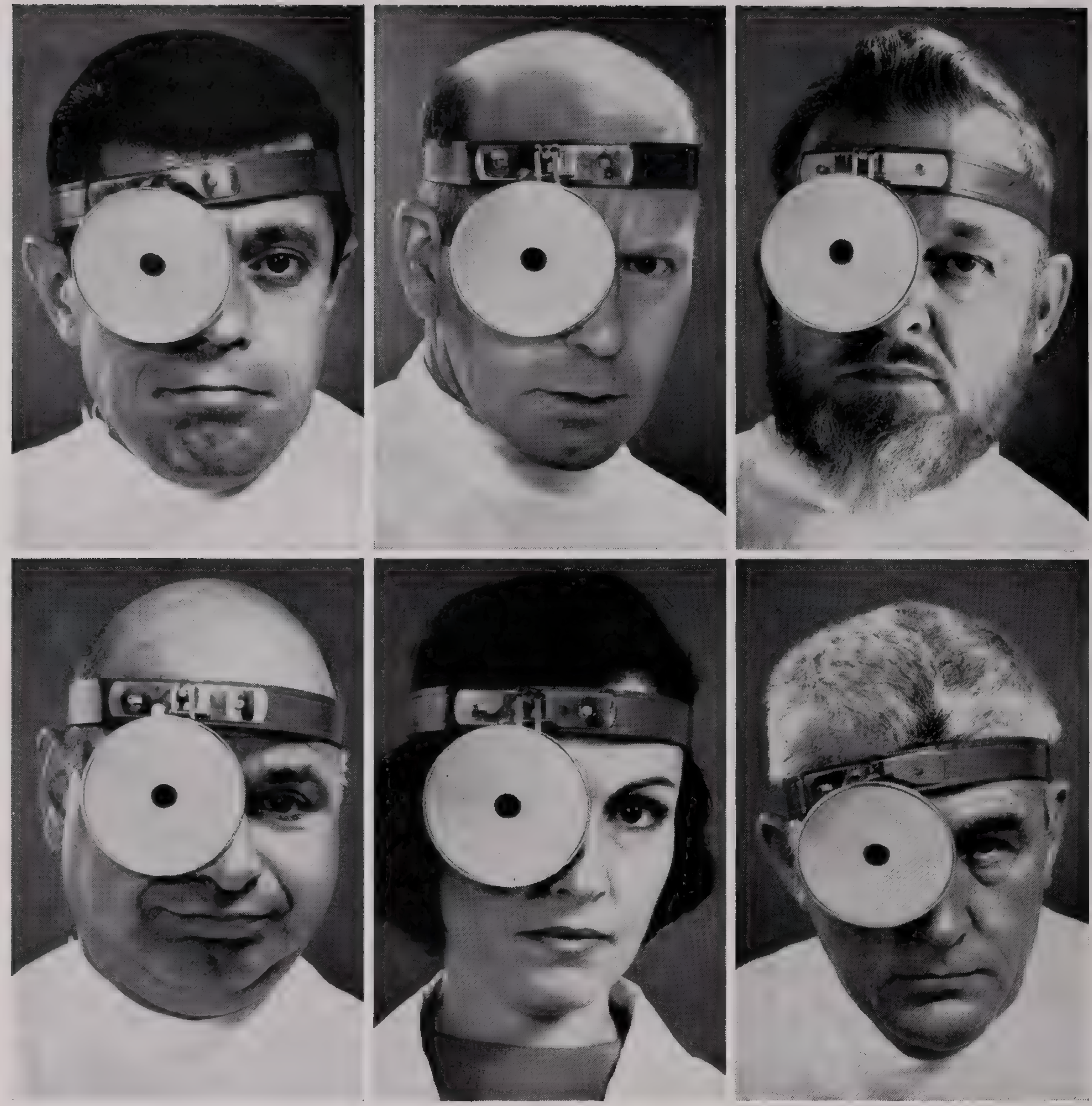

"All Otolaryngologists are Alike"

Just look at them and you can see how much they have in common. Besides, they all go through pretty much the same training, and pass the same kinds of tests, and measure up to the same sort of standards. Therefore, all otolaryngologists are alike. Right?

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You might also say that all otolaryngologists aren't alike, either.

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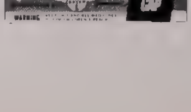


Book Reviews

Libraries are not made, they grow.—Augustine Birrell

SYNOPSIS OF SURGERY. Richard D. Liechty and Robert T. Soper; C. V. Mosby Company, St. Louis; July 1968. $12.50.

This book is a fine addition to the surgeon's bookshelf, and it is a pleasure to review it. In about 1,000 pages in pocketbook format, twenty-one authors from the University of Iowa College of Medicine have accomplished a tremendous task.

It is stated in the foreword that this book was written in regard to the changing demands of medical undergraduate education which stimulates the student to question all theories in a search for fresh answers. As more emphasis in the new curricula is placed upon clinical and bedside teaching, there is even more need to teach the basic clinical subjects as "core courses" to provide time for individual study. With this change in concept of education two different types of textbooks emerge: One designed for the student to whom the subject is fresh, new, and still unconquered; the other a reference book which discusses specific topics in substantial detail.

This book is written for the student. It covers the wide field from abdominal and thoracic surgery to the principles of neurosurgery and orthopedics, as well as touching on general biological principles, anesthesiology, and radiology. Every field seems to be covered well albeit not in depth. There are fine chapters on fluid and electrolyte management, blood transfusions, blood coagulation, wound healing, and shock.

An example of the conciseness and clarity with which this book is written is illustrated by a short paragraph entitled Spontaneous Regression of Cancer. After a short review of these occurrences, it is said: "The reason for these miraculous regressions is one of the most provocative questions in all of medicine today. Spontaneous regression of cancer strongly suggests an immune response in the host. Much current research effort is directed toward identifying and intensifying this immune response." What more needs to be said to an enthusiastic medical student!

This book does not intend to show how to do things, but what to look for and how to understand disease. Like so many of my contemporary colleagues, I have always had a folder with cutout articles, bits and pieces of useful information, tables, etc. This surgical synopsis makes it almost unnecessary to keep and maintain my favored folder which I can never find when I am in a hurry.

The price is reasonable, the text is excellent, the illustrations—including the x-ray reproductions—are of high quality, and the paper, cover, type, and general makeup of the book are quite pleasing.

Herman W. Heupel, M.D., Ph.D.
Minneapolis, Minnesota

MEDICAL PHYSIOLOGY, Edited by: Vernon B. Mountcastle, M.D.; C. V. Mosby Company, 1968; Two Volumes, 12th Edition; Price: $24.00.

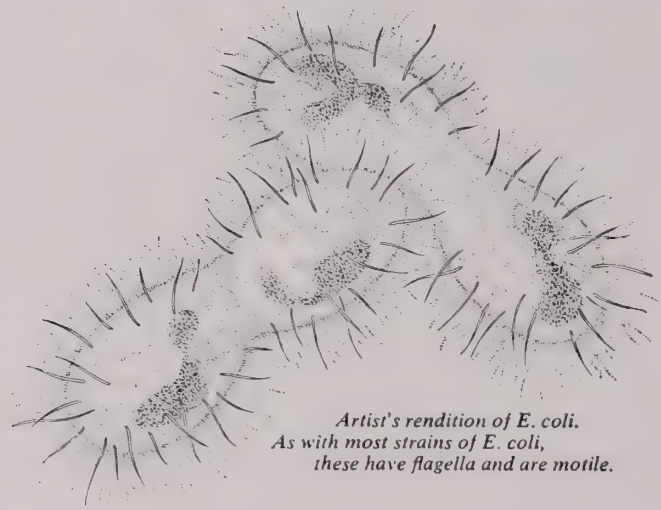
The 12th edition of this comprehensive textbook on medical physiology edited by Dr. Mountcastle of the Johns Hopkins University is brought up to date and retains the high quality and excellence of the previous editions. The text covers all areas of physiology in detail, is well illustrated, and contains key references to the medical literature. The material presented is basic normal physiology with little reference to clinical disease abnormality.

The book is intended primarily for medical students and graduate students in the field of physiology rather than as a reference source of pathophysiology for the clinician. Clinicians, however, will find the text easy to read and worthwhile for review and updating of their knowledge of physiology as a basic science. As Dr. Mountcastle states in the preface, this book is not merely a compilation of currently known facts in physiology but rather an attempt to provide the reader with a method and an attitude which, along with scholarly reflection, will serve him long after the concepts presented are replaced by new and more cogent ones.

The book is recommended to medical students, graduate students in physiology, and clinicians, as a basic science text in normal physiology.

Alvin L. Schultz, M.D.
Minneapolis, Minnesota

To help avert chronicity in acute cystitis



Artist's rendition of E. coli.
As with most strains of E. coli,
these have flagella and are motile.

Although it may coexist w
chronic pyelonephritis or pros
titis, many cases of chronic cy
tis may result from incompl
treatment of a simple, acute cy
tis. For this reason, it is be
increasingly recommended t
appropriate antibacterial thera
in full dosage be maintained
up to two weeks or longer.

Most frequently, the domina
pathogen is gram-negative, u
ally *E. coli;* most often, you v
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and other sensitive organism
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—commonly seen in cystitis a
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Wide clinical usage of Gantan
has confirmed the efficacy of t
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agent in the treatment of cystit

The rapidity of bacterial m
tiplication in a favorable urina
environment is well know
Prompt control of acute bladd
infection is therefore essent

Before prescribing, please consult co
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which follows:

Indications: Acute and chronic urina
tract, respiratory and soft tissue inf
tions due to susceptible microorganis
prophylactically following diagnostic
strumental procedures on genitourina
tract.

Contraindicated in sulfonamide-sensit
patients, pregnant females at term, p
mature infants, or newborn infants d
ing first 3 months of life.

Warnings: Use only after critical
praisal in patients with liver or re
damage, urinary obstruction or blo
dyscrasias. Deaths reported from h
persensitivity reactions, Stevens-Johns
syndrome, agranulocytosis, aplastic an
mia and other blood dyscrasias. In clos
intermittent or prolonged therapy, blo
counts and liver and kidney function te
should be performed. Clinical data ins
ficient on prolonged or recurrent thera
in chronic renal diseases of children u
der 6 years.

Precautions: Occasional failures may
cur due to resistant microorganisms. N
effective in virus and rickettsial inf
tions. Sulfonamides not recommend

ot only to reduce the patient's iscomfort but to prevent chron:city and possible ascending in:ection.

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Over eight years' clinical use as thoroughly demonstrated the ualities that make Gantanol a ood choice for initial therapy of ost urinary tract infections, inluding acute cystitis.

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or therapy of acute infections caused by roup A beta-hemolytic streptococci. At resent, penicillin is drug of choice in cute group A beta-hemolytic streptococal infections; although Gantanol has roduced favorable bacteriologic converon rates in this infection, data insuffient on long-term follow-up studies as to s effect on sequelae of rheumatic fever r acute glomerulonephritis. If other eatment cannot be used and Gantanol employed in such infections, *important at therapy be continued in usual recmmended dosage for at least 10 days.* bserve usual sulfonamide therapy preutions, including adequate fluid intake. se with caution if history of allergies nd/or asthma. Follow closely patients ith renal impairment since this may use excessive drug accumulation. Need r indicated local measures or surgery ot obviated in localized infections.

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Cyanocobalamin	2.5 mcg.	1.5 mcg.
Intrinsic factor concentrate	8.0 mg.	–
Thiamine HCl	–	5.0 mg.
Thiamine mononitrate	10.0 mg.	–
Riboflavin	5.0 mg.	–
Niacinamide	50.0 mg.	–
Pyridoxine HCl	3.0 mg.	–
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Medicine and History

Dostoevsky's Pulmonary Disease

Physician readers justifiably might ask why anyone in medicine would be interested in Fyodor Michailovich Dostoevsky. Certainly Dostoevsky was a very interesting and complex man but, specifically, this communication concerns his pulmonary disease which seems to have escaped medical attention. Dostoevsky manifested many problems of consuming interest to psychiatrists and neurologists, but perhaps there was one problem to evoke the interest of specialists in pulmonary disease as well.

Biographies of Dostoevsky usually recount the tempestuous life of this great writer, his neurotic temperament, his Siberian prison experiences, his obsessive gambling, and his epilepsy. He was the son of a physician. The murder of his father by the serfs was cited by Freud as the genesis of an oedipal guilt which affected Dostoevsky's entire life and purportedly is reflected in his works. His personal problems were quite intriguing, but it was a surprise to me to discover that the cause of his death had no relation to his epilepsy but was rather the consequence of an 11-year course of progressive pulmonary disease.

Dostoevsky died in St. Petersburg (Leningrad) on January 28, 1881, in his 60th year. Because several available biographies indicated he had coughing, wheezing, and dyspnea, it became a challenge to delve into the medical aspects of the terminal years of his life.

The last three years of Dostoevsky's life[1] were only rarely marred by grand-mal epileptic seizures. However, his worsening dyspnea, cough, and hoarseness have been described. According to a letter from N. V. Shakhalova (personal communication, April 1968) of the Dostoevsky Museum in Moscow, Dostoevsky's pulmonary disease appeared around 1870. Because of it he made several visits to a health resort in Ems, Germany. In 1878, at the request of his second wife, Anna, Dostoevsky was examined by Dr. M. N. Snitkin, a relative of hers. Dr. Snitkin diagnosed emphysema of a rapidly progressive type and cautioned about the danger of rupture of pulmonary blood vessels.

Mochulsky, in describing the public appearances during Easter, 1879, stated: "These public appearances caused him great strain; he was suffering from emphysema, easily lost his breath, controlled his breath with muted and hoarse voice with difficulty." This quotation suggests that dyspnea and speaking were more of a problem than was coughing. The following is from a letter* (translated) written by Dostoevsky at Ems to his wife on July 25, 1879:

> Yesterday I went to [Dr.] Ort; after three years he immediately recognized me. He examined me thoroughly. He said that it is emphysema but still in its beginning and although it is impossible to cure it, it can be treated with great and significant success. That you did not come in three years strengthens the action of Krenken (mineral water) and in Krenken you will revive. But in the beginning we will use Krenken and later we will try Kesselbrunnen

---

*Supplied by the Dostoevsky Museum, Moscow.

> (also a mineral water). He found that I had some type of change in the lungs and the heart, all the consequences of emphysema.

The above letter suggests that the physicians thought that their patient had pulmonary hypertension. This is in accord with the opinion of Dr. Snitkin, particularly concerning the possibility of a pulmonary hemorrhage. The way the letter is worded also suggests the possibility of pulmonary fibrosis.

Mochulsky stated that:

> On the night of January 25 to 26 [1881] while working in his study he began to cough blood. The extravasation was so insignificant he paid no attention; on January 26 there were two new hemorrhages. The doctor was summoned. The patient lost consciousness.

Another account of this event is translated from a book by L. Grossman[2] published in Moscow in 1965.

> Dostoevsky arose from behind the table and went to his study. Here he had a gushing forth of blood from his throat but this did not last long. He attempted to calm his family and showed the children inscriptions in the journal "Chips" with humorous pictures and verses.

Apparently the hemorrhages recurred the evening of the 26th; so Dr. Koshlakov* was summoned, who, following his examination, diagnosed the condition as rupture of a small vessel and not likely to be serious. On January 27th Dostoevsky spent a comfortable day. He received a few friends and read to his children, but he awoke in the early hours on January 28th with an overwhelming premonition of his impending death. As translated from Grossman's book: "In the 11th hour, throat hemorrhages recurred. The patient felt unusual weakness. . . . After a new hemorrhage at the 7th hour in the evening, he lost consciousness and died at 8:38 p.m."

There is no report of an autopsy, and we have no access to records that will throw any additional light on these final days. Since reports of the physicians who attended Dostoevsky in his final days are unavailable in this country, we are left to speculation.

My colleagues in the specialty of pulmonary disease assure me it would be most unusual for hemoptysis to occur with emphysema. We know that Dostoevsky was a heavy smoker of cigarettes and cigars virtually all of his life. The diagnosis of emphysema therefore would be in accord with this information. Is it possible also that chronic bronchitis or even bronchiectasis may have developed? Pulmonary hemorrhage can occur in bronchiectasis; therefore, this must be considered as a diagnostic possibility. We also know that he was given positive-pressure breathing treatments of some sort during his stay at Ems on at least one occasion.

Consideration of pulmonary carcinoma seems rather unfounded in view of his health and relative vigor up until the last few days of his life. In other words, from all evidence at hand, he did not deteriorate physically or mentally and was active in both writing and in conferring with his publishers. However, there does seem to be another possibility, particularly in view of its prevalence in Russia 100 years ago—pulmonary tuberculosis.

Dostoevsky's mother died of tuberculosis, as did his first wife. No doubt he was also intimately exposed to tuberculosis during his four years in a Siberian prison camp. It seems odd that nowhere has this diagnosis been mentioned in the references examined. It also seems unlikely that a diagnosis of pulmonary tuberculosis would have eluded the physicians who treated him, familiar as they were with the disease at that time. No mention was found in the sources examined regarding expectoration or medications.

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*According to a personal communication from L. Pantserova, February 1968.

It seems most probable to me that tuberculosis played the major role in Dostoevsky's death. It also seems reasonable that Dostoevsky had chronic pulmonary disease, perhaps even emphysema, but developed pulmonary tuberculosis with cavity formation. Tuberculous erosion of a vessel could therefore have produced the hemoptysis which resulted in his death.

Edmund C. Burke, M.D.*
Rochester, Minnesota

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*Mayo Clinic and Mayo Foundation: Section of Pediatrics.

References

1. Mochulsky, K. V.: Dostoevsky: His Life and Work (Translated by M. A. Minihan), Princeton, New Jersey: Princeton University Press, 687 pp., 1967.
2. Grossman, L.: Dostoevsky (Russian.), Moscow: Izdatelstvo, USSR, 604 pp., 1965.

John A. Tobin, M.D.

Doctor Tobin took the cover picture while on vacation in Western Montana. He was driving along the highway around 4 o'clock in the afternoon and came upon this beautiful scene at a bend in the road.

Born in Mitchell, South Dakota, Dr. Tobin attended Creighton University Medical School in Omaha, Nebraska, and his residency training was taken at the University of Michigan. He is a member of Radiologist Consultants and is on the radiology staffs of five metropolitan hospitals.

T.B. and Big Shots

The list of those afflicted with tuberculosis leads me to conclude that here is the most admirable of all diseases. Termed "The Great Destroyer", T.B. seems to have contributed more to the world's knowledge and enjoyment of life than all the nondestructive, beneficial agencies put together—assuming that the psychologists are right in their theory that T.B. inspires men to improve themselves. Although some famous T.B.-ers died young, the majority lived as long as the average citizen of their times in spite of the fact that nobody knew how to cure T.B. then.

Moliere was fifty-one when he died in harness shortly after collapsing on the stage during the opening performance of *Le Malade Imaginaire.* Sir Walter Scott recovered from T.B. as a young man and went on to turn out almost as much fiction as Edgar Wallace. Goethe had T.B. for a while and undoubtedly it shortened his life to a mere eighty-two years. Voltaire was never free of it and so he tossed in the sponge at eighty-three. Ralph Waldo Emerson, a typical T.B.-er in every physical respect, benefited humanity by living and working for nearly eighty years. Balzac, like Moliere, died probably of T.B. at 51, but by that time he had written more novels than any single man was apt to read. Just before he died, he took himself a wife, so maybe the T.B. wasn't entirely to blame.

Paganini, Laennec, Raphael, Watteau, John Calvin, Henry Thoreau, Merimee, Laurence Sterne, Robert Louis Stevenson, Schiller, Spinoza—all these allegedly suffered from T.B.*

---

*Sprague, Marshall: The Business of Getting Well, 1943.

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high under the cuff.

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Warning: With the administration of enteric-coated potassium supplements, which should be used only when adequate dietary supplementation is not practical, the possibility of small-bowel lesions (obstruction, hemorrhage, and perforation) should be kept in mind. Surgery for these lesions has frequently been required and deaths have occurred. Discontinue coated potassium-containing formulations immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occur. Discontinue one week before electroshock therapy, and if depression or peptic ulcer occurs.
Use in pregnancy: Because chlorthalidone may cross the placental barrier and appear in cord blood and thiazides may appear in breast milk, this drug should be used with care in pregnant patients and nursing mothers. When used in women of childbearing age, the potential benefits of the drug should be weighed against the possible hazards to the fetus. Use of chlorthalidone may result in fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. Increased respiratory secretions, nasal congestion, cyanosis and anorexia may occur in infants born to reserpine-treated mothers.
Precautions: Antihypertensive therapy with this drug should always be initiated cautiously in postsympathectomy patients and in patients receiving ganglionic blocking agents, other potent antihypertensive drugs, or curare. Reduce dosage of concomitant antihypertensive agents by at least one-half. To avoid hypotension during surgery, discontinue therapy with this agent two weeks prior to elective surgical procedures. In emergency surgery, use, if needed, anticholinergic or adrenergic drugs or other supportive measures as indicated. Because of the possibility of progression of renal damage, periodic kidney function tests are indicated. Discontinue if the BUN rises or liver dysfunction is aggravated. Hepatic coma may be precipitated. Electrolyte imbalance, sodium and/or potassium depletion may occur. If potassium depletion should occur during therapy, the drug should be discontinued and potassium supplements given, provided the patient does not have marked oliguria.
Take particular care in cirrhosis or severe ischemic heart disease and in patients receiving corticosteroids, ACTH, or digitalis. Severe salt restriction is not recommended. Use cautiously in patients with ulcerative colitis or gallstones (biliary colic may be precipitated). Bronchial asthma may occur in susceptible patients.
Adverse Reactions: The drug is generally well tolerated. The most frequent side effects are nausea, gastric irritation, vomiting, diarrhea, constipation, muscle cramps, headache, dizziness and acute gout. Other potential side effects include angina pectoris, anxiety, depression, bradycardia and ectopic cardiac rhythms (especially when used with digitalis), drowsiness, dull sensorium, hyperglycemia and glycosuria, hyperuricemia, lassitude, restlessness, transient myopia, impotence or dysuria, orthostatic hypotension which may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics, leukopenia, aplastic anemia, skin rashes, thrombocytopenia, agranulocytosis, nasal stuffiness, increased gastric secretions, nightmare, purpura, urticaria, ecchymosis, weakness, uveitis, optic atrophy and glaucoma, and pruritus. Eruptions and/or flushing of the skin, a reversible paralysis agitans-like syndrome, blurred vision, conjunctival injection, increased susceptibility to colds, dyspnea, weight gain, decreased libido, dryness of the mouth, deafness, anorexia, and pancreatitis when epigastric pain or unexplained G.I. symptoms develop after prolonged administration. Jaundice, xanthopsia, paresthesia, photosensitization and necrotizing angiitis are possible.
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Availability: Pink, single-scored tablets in bottles of 100 and 1000.
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RE-6392

MINNESOTA STATE MEDICAL ASSOCIATION
116TH ANNUAL MEETING MAY 26 • 27 • 28, 1969
CONVENTION HALL, MINNEAPOLIS AUDITORIUM
"THE UPPER-MIDWEST'S GREAT MEDICAL MEETING"

All under one roof . . .

THINGS WERE bound to happen when our energetic Committee on Scientific Assembly decided to devote its efforts to plan an annual meeting scientific program with a new twist.

A series of 32 workshops have been scheduled to highlight the 116th Annual Meeting of the Minnesota State Medical Association May 26, 27 and 28 in the new Minneapolis Auditorium Convention Hall. The spacious new Convention Hall will house all major scientific and most business sessions of the meeting. This arrangement will make it possible for physicians to attend the meeting without spending valuable time getting to and from events scheduled at remote locations.

The workshop innovation will replace the customary programs on Monday and Tuesday afternoons and Wednesday morning. Each workshop will be repeated twice—in sessions lasting from 2:00 to 3:00 P.M. and 3:45 to 4:45 P.M. on Monday and Tuesday and 9:30 to 10:30 A.M. and 11:00 to 12:00 noon on Wednesday. This arrangement will make it possible for physicians to attend workshops of their preference with a minimum amount of conflict. Everyday problems encountered by the practicing physician will be given preferential treatment by speakers selected primarily from the ranks of eminent Minnesota specialists and consultants.

The new format is based on the results of nearly a year of exploration of a number of possibilities, including a study of some of the most successful medical meetings in the nation, conducted by the Committee and its Chairman, Doctor O. L. N. Nelson.

"Hand Injuries—13 Things to Avoid," "Drugs for Nervousness," "Menopause—an Organic vs. a Psychiatric Problem," "The New Diuretics," "Thyroid Disease—A Therapeutic Controversy," are among the topics selected for presentation at the 32 workshops.

"In depth" discussion of two major subjects have been scheduled for Monday and Tuesday morning. "Fluids & Electrolytes—How Much, What Kind and When" will be discussed Monday, May 26, at 9:30 A.M. by Doctor William E. Segar, Rochester. His paper will be concerned with the presentation of a simple usable system of parenteral fluid therapy. Emphasis will be placed upon avoiding complications that might prove fatal to the child.

"Cancer Chemotherapy" will be the subject of the Tuesday "in depth" presentation scheduled to begin at 9:30 A.M., arranged by Doctors David Ahmann and J. M. Kiely, both of Rochester. The topics are "The Chemotherapy of Solid Tumors in Children," "The Chemotherapy of Gastrointestinal Cancer," "Progress in the Management of the Patient with Lymphoma," "Current Thoughts About the Chemotherapy of Leukemia," "Testicular Cancer—Current Chemotherapy," and "The Medical Management of Disseminated Breast Cancer."

Two major luncheon meetings have been scheduled for Monday and Tuesday noon at the Minneapolis Auditorium Convention Hall. On Monday, May 26, Doctor A. C. Aufderheide, Duluth, will discuss his trip "To the North Pole by Snowmobile." Physicians are encouraged to bring their wives to this event. "Alcoholism" will be the topic of discussion at the Tuesday luncheon. The presentation will be made by the Reverend Philip L. Hansen, White Bear Lake. Reverend Hansen is chairman of the Minnesota Commission on Alcohol Problems.

The House of Delegates will convene Sunday, May 25, at 2:00 P.M. The second session of the House will be called to order Tuesday, May 27, at 7:00 P.M. Both sessions will be held at Holiday Inn Central.

Reference Committee meetings of the House of Delegates will be held Sunday at 8:00 P.M. and again Monday morning at 9:30 A.M. (if necessary) at the Holiday Inn Central.

A majority of the scientific and non-scientific committees of the Association have scheduled breakfast meetings, and committee members are urged to make necessary reservations to attend meetings in which they have an interest.

The Annual Banquet will be held Monday evening at 7:00 P.M., another change from the traditional Tuesday date. Outstanding entertainment and the customary awards will highlight the banquet program.

The Delegates, New Members, Officers and Sportsmen's dinner will be held Sunday evening at 6:00 P.M. following the opening meeting of the House of Delegates.

Because most of the Annual Meeting activities will be held in the Minneapolis Auditorium Convention Hall, physicians will have more time to visit the many excellent scientific and technical booths. All physicians attending the meeting are invited to visit the technical exhibits and extend their appreciation to the representatives of the firms who have participated in this meeting, thus insuring future meetings for our Association.

Future Annual Meeting information, including the official program and necessary registration materials, will be mailed to all members.

The Woman's Auxiliary will meet in conjunction with the Annual Meeting of the Minnesota State Medical Association. Hosts for this year's events are the members of the Hennepin County Medical Society and Auxiliary.

Physicians are encouraged to pre-register by completing the registration card enclosed with current issues of the Newspage and the official Annual Meeting program mailed to all members. By completing and returning this card by May 5 to the State Office, they can be certain that their badges will be waiting for them at the advance registration desk in the Minneapolis Auditorium Convention Hall.

The best way to get ahead is to have one.—Pure Globe

Time Table for Workshops

HOUR	Monday, May 26	HOUR	Tuesday, May 27	HOUR	Wednesday, May 28
Workshops given simultaneously. Each topic presented twice. First time: 2:00 to 3:00 p.m. Second time: 3:45 to 4:45 p.m.	"What to Do Until the Psychiatrist Comes" Thomas Burton Minneapolis	Workshops given simultaneously. Each topic presented twice. First time: 2:00 to 3:00 p.m. Second time: 3:45 to 4:45 p.m.	"Children Who Don't Grow" A. B. Hayles Rochester	Workshops given simultaneously. Each topic presented twice. First time: 9:30 to 10:30 a.m. Second time: 11:00 to 12:00 p.m	"Prevention of Rh Disease" H. F. Polesky E. B. Berglund A. R. Thelemann Minneapolis
	"Anesthesia and Pulmonary Disease" Hugh D. Westgate Minneapolis		"Anesthesia and Patient Monitoring" J. J. Buckley Minneapolis		"Computer Applications in Medical Practice" J. A. Hilger St. Paul
	"Drugs for Nervousness?" Burtrum Schiele Minneapolis		"Thyroid Disease—A Therapeutic Controversy" A. L Schultz F. C. Goetz F. Raymond Keating O. H. Beahrs Arnold Kremen Minneapolis		"Fertility and Infertility" John Sciarra Minneapolis
	"Preventing Complications of Acute Meningitis" M. R. Gomez Rochester		"Clotters and Bleeders" J. Roger Edson Paul R. Finley Minneapolis		"Abdominal Pain" Lyle J. Hay Minneapolis
	"Current Status of Organ Transplantation" J. S. Najarian Minneapolis		"Belchers and Bloaters" W. D. Blackwood M. D Levitt Minneapolis		"Practical Management of Acute Head Injuries" R. F. Galbraith E. S. Wisiol Minneapolis
	"Hemorrhoids—To Operate or not to Operate, That May Be the Question" Clyde E. Culp Rochester		"Chest Injuries" Richard E. Larson Minneapolis John Culligan, St. Paul Josiah Fuller, Duluth		"Nonsuture Technique in Surgical Treatment of Varicose Veins" D. A. Felder St. Paul
	"Cutaneous Patterns of Fatal Disease" R K. Winkelmann Rochester		"Reflux and the Assaulted Kidney" G. W. Koos Minneapolis		"Anesthesia in the Office and Emergency Room" J. W. Smith St. Cloud
	"Hand Injuries—13 Things to Avoid" Kenath H. Sponsel Minneapolis		"Menopause—An Organic vs. a Psychiatric Problem?" Bruce F. P. Williams Duluth		"The New Diuretics" D. A. Duncan Minneapolis
	"Thyroid Function Testing—An Exercise in Medical Detection" C. A. Gorman Rochester		"Rheumatism and Drugs" Paul Andreini Rochester		"Pulmonary Insufficiency" W. A. Corson R. V. Ebert Minneapolis
	"Burns—How to Treat Them" J. W. LaFave St. Paul		"The Threatening Eye" William Slack Duluth		"Saving the Cold and Pulseless Limb" Yoshio Sako Carl Manz Minneapolis
	"Multiple Injuries" John F. Perry, Jr. St. Paul		CCU ECG Group Problem Solving Sessions Gerald Lee, St. Paul		

During Intermission Visit Exhibits

Rehabilitation Medicine

A Decade of Progress

REHABILITATION MEDICINE as an in-patient hospital specialty developed in the military hospitals of the Second World War and continued to grow during the poliomyelitis outbreaks of the next ten years. A new body of knowledge concerning the management and treatment of chronic neuromuscular problems accumulated around techniques of muscle strengthening and re-education, range of motion exercises, and therapeutic physical agents.

By the time poliomyelitis was eliminated as a major crippler, rehabilitation medicine had already begun to adapt the concepts and techniques it had developed for the management and treatment of that disease to other disabling conditions. Hemiplegia, paraplegia, quadriplegia, multiple sclerosis, lower motor neuron disease, and cerebral palsy all fit into the category of chronic neuromuscular disability, and the concern of rehabilitation centers shifted to patients with these problems, plus arthritics and amputees.

Present Trend

In the decade since rehabilitation medicine made the transition from polio to these other diseases, a new look has become apparent in the field. The complex disease processes being treated require comprehensive management; the rehabilitation team has become the most prominent aspect of rehabilitation medicine. Not only the patient but his family and community are involved in evaluation, diagnosis, and treatment. The patient's social, environmental and vocational problems as well as his physical limitations are dealt with by such paramedical personnel as psychologists, social workers, speech pathologists, audiologists, etc.

With the increased severity of involvement and the greater utilization of paramedical personnel, the rehabilitation process has become more time-consuming and costly. Rising rates for standard hospital services, added to the cost of comprehensive complex care, have put rehabilitation beyond the reach of the individual, unless he has extraordinary third-party coverage or large independent financial resources. Thus, rehabilitation centers have found it necessary to subsidize their services in order to avoid placing undue financial burdens on the patient. No comprehensive rehabilitation center in the United States operates without a substantial financial loss. Paradoxically, the more efficient and effective the center's treatment of the chronic-disease patient, the larger the deficit. This is a result of increased paramedical personnel costs and decreased number of total patient days.

Changes in Length of Hospital Stay

Just how effective has the rehabilitation process become, and what standards do we have for tracing the changes in its performance? A recent survey at the Kenny Rehabilitation Institute revealed the following facts:

In 1959 the average length of stay at Kenny Rehabilitation Institute was 52.3 days. The diagnostic categories treated were:

Hemiplegia	47%
Paraplegia and quadriplegia	6%
Cerebral palsy	15%
Rheumatoid arthritis	12%
Amputations	0%
Mixed neurological categories (including multiple sclerosis, muscular dystrophy, amyotrophic lateral sclerosis, Guillain-Barre syndrome, and some post-poliomyelitic residuals)	21%

In 1967 the average length of stay at Kenny Rehabilitation Institute was 29.6 days. The diagnostic categories treated were:

Hemiplegia	32%
Paraplegia and quadriplegia	19%
Cerebral palsy	23%
Rheumatoid arthritis	10%
Amputations	10%
Mixed neurological categories	6%

The diagnostic categories are the same, except that amputations are now included. Nor has there been any major change in the distribution of cases among the categories; there has been some increase in spinal cord injuries and some decrease in stroke, but the mix is fairly similar.

The important difference is the decrease in length of stay. It should be emphasized that both sets of figures refer to patients who entered the hospital with comparable degrees of disability and who had achieved similar levels of improvement at the time of discharge. Despite the increase in the number of paraplegics and quadriplegics, whose rehabilitation requires longer periods of time than that of patients in other categories, the patient's time in hospital was reduced by 1967 to little more than half the duration in 1959.

This decline has been reflected in all the diagnostic categories. In 1959 the average length of stay for a hemiplegic patient was 53.7 days. By 1964 this had decreased to 36.7, and by 1967 to 29.5 days. Paraplegic and quadriplegic patients, whose rehabilitation 10 years ago required six to nine months, now require about four months to attain the same degree of improvement. These two categories account for the majority of patients in an intensive rehabilitation center, but similar decreases are recorded in the other categories.

Quality of Care

Sheps[1] has pointed out that there are four methods of approaching the problem of quality control in the area of medical care. They are: (1) selected prerequisites or standards; (2) indexes, or components of the process; (3) evaluations of clinical performance by expert judges; and (4) indexes of the effects of care on patients. As Ellwood has remarked,[2] only the last is actually a measure of "the true goal—the outcome of medical care," and it is not often used in nonfatal processes.

When outcome criteria are used in rehabilitation medicine, they are often based on subjective appraisals of improvement. This approach has proved somewhat less than satisfactory, because of the chance of misinterpretation by the evaluator when he assesses improvement or change in the patient, and because of the general unreliability of non-objective criteria. Many rehabilitation centers have utilized objective rating scales to determine functional mobility and self-care capabilities. These scales enable the specialist in rehabilitation medicine and the rehabilitation team to assess their therapeutic techniques better, and also to compare various treatments.

At the Kenny Rehabilitation Institute, rating scales have been developed[3] which accurately measure the self-care status of patients. Each of 17 activities is rated on a five-point scale, and each point on the scale is explicitly and operationally defined in terms of how much assistance the patient needs in order to perform the activity. High inter-observer reliability has been shown to exist in the scoring.[4]

Using this self-care assessment as the criterion measure, researchers at Kenny have sought to develop prediction criteria that can be applied upon admission, as soon as the pertinent data have been gathered.[4] The capability of setting goals which are realistic and attainable for the individual patient conserves the time and effort of the rehabilitation team, saves excessive cost, and limits the patient's rehabilitation process to a definable period of time.

The Future

We feel a certain sense of accomplishment in the expeditiousness with which patients in the disease categories mentioned earlier are now being rehabilitated, but at the same time we are looking ahead to a new decade which will bring an expansion in the scope of rehabilitation services.

With objective criteria we can now apply the skills of rehabilitation medicine to more obscure and diffuse diagnostic categories which include diminished functional capabilities among their effects, such as mental retardation, learning disorders, emotional disturbances, and diseases of the geriatric population.

We must also be more selective in our treatment programs, improving our utilization of scarce professional personnel. By the use of objective outcome criteria, therapeutic emphasis can be placed at appropriate times during the course of the patient's illness and rehabilitation. We must select the optimum points of intervention in this process and assign the specialized therapies which will enable the patient to make the most rapid progress possible.

The tools of the electronic communication systems adapt themselves well to the field of rehabilitation medicine, providing rapid and accurate dissemination of information to communities and units which are not large enough to support an intensive rehabilitation center. Television consultation, computer data pools, and electronic treatment simulation systems will become practical tools for both the rehabilitation specialist and the family physician. In the coming decade, disability—physical, social, and vocational—may be treated as aggressively as acute disease.

Loren R. Leslie, M.D.*
Minneapolis, Minnesota

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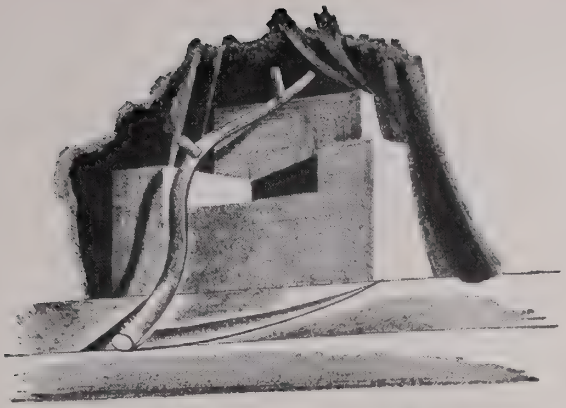
*Director, Kenny Rehabilitation Institute.
References may be secured from the author or the reprints.

Smokers and non-smokers cannot be equally free in the same railway carriage.—
George Bernard Shaw



In Memoriam

Death, so called, is a thing which makes men weep,
And yet a third of life is pass'd in sleep.
—*Byron*

LAWRENCE M. RANDALL, M.D.

Dr. Lawrence M. Randall, 73, nationally-known specialist in obstetrics and gynecology, died January 11. He had retired in 1960 after a 34-year career at the Mayo Clinic.

Born in LaMoille, Iowa, Dr. Randall received his medical degree from the State University of Iowa. He came to Rochester in 1924 and was appointed to the staff of the Mayo Clinic in 1926. In 1946 he was elected president of the Clinic staff and became a member of the board of governors in 1948. Dr. Randall served as president of the American Association of Obstetrics and Gynecology in 1954 and also as president of the Minnesota Society of Obstetrics and the Central Association of Obstetricians and Gynecologists.

Dr. Randall was a member of the Zumbro Valley Medical Society and the American Medical Association and an Associate Member of the Minnesota State Medical Association.

He is survived by his wife, a daughter, and two sons, one of whom is Dr. David Randall of Minnetonka.

NORMAN LENDE, M.D.

Dr. Norman Lende, 72, retired staff member of the Faribault State School and Hospital, passed away January 21. He had been ill for over a year.

Dr. Lende graduated from the University of Minnesota Medical School in 1928, interned at St. Mary's Hospital in Duluth, and was a member of the Alpha Omega Alpha Fraternity. He was also a member and past president of the Rice County Medical Society, a member of the American Medical Association and an Associate Member of the Minnesota State Medical Association.

Dr. Lende is survived by his wife and daughter.

JOHN H. GRINDLAY, M.D.

Dr. John H. Grindlay, 59, member of the Mayo Clinic's staff and head of the surgical research section, died December 14.

A native of Philadelphia, he received his Medical degree from the Harvard Medical School in 1935 and came to Rochester as a Mayo Graduate School resident in 1937. He was a member of the Zumbro Valley Medical Society, the American Medical Association and an Associate Member of the Minnesota State Medical Association.

Dr. Grindley is survived by his wife, two daughters and one son.

WALLACE P. RITCHIE, M.D.

Dr. Wallace P. Ritchie, 63, St. Paul surgeon, died January 22 during the night of a heart ailment. He was a life-long resident of St. Paul and began practicing medicine in the city in 1932. He was a graduate of Yale University and Johns Hopkins University, obtaining his medical degree at Johns Hopkins.

Dr. Ritchie was a past president of the St. Paul Surgical Society and was on the board of governors of the American College of Surgeons. He was a member of the Ramsey County Medical Society, the American Medical Association and the Minnesota State Medical Association.

He is survived by his wife and three sons.

HARRY LEROY SMITH, M.D.

Dr. Harry LeRoy Smith, widely-known specialist in diseases of the heart at the Mayo Clinic and emeritus professor of medicine in the Mayo Graduate School of Medicine, died in the La Mesa Hospital in La Mesa, California, February 13.

Born in Fairport, Missouri, he obtained his degree of doctor of medicine in 1916 from the State University of Iowa. In 1928 he was appointed to the staff of the Mayo Clinic.

Dr. Smith was certified as a specialist in cardiovascular diseases by the American Board of Internal Medicine, was a fellow of the American College of Physicians, a former president of the Zumbro Valley Medical Society, member of the Minnesota Society of Internal Medicine, the Minnesota Heart Association, the American Heart Association, the American Medical Association and a 50 Club and Associate Member of the Minnesota State Medical Association.

He is survived by his wife, one daughter, and a son, Dr. Meredith P. Smith of Seattle, Washington.

CLARENCE WILLIAM MOBERG, M.D.

Dr. Clarence Moberg, 66, prominent state physician and resident of Detroit Lakes for the past 34 years, died March 1, after a two-year illness. He is credited with originating the Minnesota Blue Shield Health Insurance Program and the Becker County Blood Bank.

He was a former vice president of the Minnesota State Board of Medical Examiners, vice president of the Minnesota State Medical Association, member of the American Academy of General Practitioners, member of the Clay-Becker County Medical Society, and a member of the American Medical Association.

He is survived by his wife, a daughter, and two sons, one of whom is Dr. Allen Moberg of Minneapolis.

HEWITT B. HANNAH, M.D.

Dr. Hewitt B. Hannah, 72, Minneapolis psychiatrist and neurologist, died February 7. He attended Miami University in Oxford, Ohio, and graduated from the University of Cincinnati Medical School. At the time of his death he was on the staffs of Northwestern, Abbott and St. Barnabas Hospitals.

Dr. Hannah was a member of the American Medical Association, the Minnesota State Medical Association, the Hennepin County Medical Society, the American Psychiatric Association, the Neuro-Psychiatric Society, the Central Electroencephalographical Society, the Minneapolis Academy of Medicine and the Minnesota Society of Neurology and Psychiatry.

He is survived by his wife, a daughter, and a son.

NABOTH O. PEARCE, M.D.

Dr. N. O. Pearce, 89, one of the first pediatricians to practice in Minneapolis, died March 5, in Tavernier, Florida. A graduate of the University of Minnesota Medical School, Dr. Pearce practiced in Minneapolis from 1914 to 1968.

He was a past president of the Minnesota State Medical Association, the Hennepin County Medical Society and the Hennepin County Tuberculosis Association. Dr. Pearce was also a member of the American Medical Association.

He is survived by his wife and one son.

WILLIAM L. BENEDICT, M.D.

Dr. William L. Benedict, head of the Section of Ophthalmology of the Mayo Clinic from 1917 to 1949, died February 18 at the age of 84. Born in Springport, Indiana, he received his medical degree from the University of Michigan.

He was a member of the American Board of Ophthalmology, founder of the American Board of Opticianry and chairman of its Advisory Committee, fellow of the American College of Surgeons, former president of the American Ophthalmological Society, former vice president of the Pan-American Association of Ophthalmology, former chairman of the American Medical Association's Section of Ophthalmology, former member of the House of Delegates of the American Medical Association, executive secretary-treasurer of the American Academy of Ophthalmology and editor-in-chief of the bimonthly *Transactions* of the Academy. Dr. Benedict was a member of the editorial boards of six other scientific journals and a member or honorary member of numerous scientific societies.

He is survived by his wife, two daughters, and a son, Dr. Walter Benedict of Knoxville, Tennessee.

They Never Quite Leave Us

They never quite leave us, our friends who have passed
Through the shadows of death to the sunlight above;
A thousand sweet memories are holding them fast
To the places they blessed with their presence and love.
The work which they left and the books which they read
Speak mutely, though still with an eloquence rare,
And the songs that they sang, the words that they said,
Yet linger and sigh on the desolate air.
And oft when alone, and oft in the throng,
Or when evil allures us, or sin draweth nigh,
A whisper comes gently, "Nay, do not the wrong,"
And we feel that our weakness is pitied on high.

—**Margaret E. Sangster**

Address

Opportunity Unlimited*

HAROLD S. DIEHL, M.D.
New York, New York

DEAN HOWARD, members of the Medical Faculty, the graduating class of 1968, families and friends: To the graduating class, my greetings and congratulations. You have successfully completed a long and difficult program of preparation for the practice of your chosen profession. You have every reason to feel gratified.

It was on June 20, 1918, that the University of Minnesota awarded me a Doctor of Medicine degree. Nineteen sixty-eight is therefore the 50th anniversary of my graduation from Medical School. The realization of this is thrilling but sobering. For me 1968 is a year of another anniversary; for it was ten years ago that I retired as Dean of the Medical Sciences to accept a position on the National staff of the American Cancer Society.

Fifty years, even ten years, are a long time. It is heartwarming *not* to be forgotten with the passing of these years. Also pleasing was the invitation to participate in this program, the fiftieth year of my own graduation.

I received my medical degree in 1918; but I did not attend my graduation ceremony, escaping that by going to France with the U. S. Army to help make the "world safe for democracy." The reason we were able to leave the University before the end of our senior year was that the Medical Faculty granted us permission to enlist in a base hospital unit that was being organized by the University and staffed jointly by the Medical School and the Mayo Clinic. Little did I dream then that 25 years later as Dean of the Medical School I would be responsible for the organization of a similar hospital unit to serve in World War II; nor that 50 years later I would be talking to a graduating class faced with the possibility of service in another war to make a small country on the other side of the world "safe for democracy."

I am sure that few if any college graduates remember what was said in the addresses delivered at their commencement exercises, or even who the speaker was. Dr. Alan Gregg, long-time Director for Medical Sciences of the Rockefeller Foundation, used to say: "If you want people to remember what you say, tell them a story." I am not going to tell you a story but rather the main theme, as I remember it, of an address given here about fifteen years ago by Dr. Robert Newell, the wise and distinguished Professor of Radiology at Stanford University. The occasion was the dedication of the Mayo Memorial Building. The title of the address was "Mink Coats and Cadillacs." We were surprised when Dr. Newell submitted that title and wondered what he would say. His address was deadly serious. He talked about the priceless rewards that a physician receives from his work. To illustrate, Dr. Newell said that each day on his way to the University Hospital in San Francisco he walked through several blocks of slums occupied mostly by Negroes and Mexicans. And along the way he always noticed several second-hand Cadillacs spotlessly clean and beautifully polished. One's natural reaction, he said, is to criticize anything so out-of-keeping with the environment. But, he continued, we should not do so. Everyone needs something in which he can take pride, something to bolster his ego, to nourish his soul. The men who own and polish these Cadillacs live in a ghetto; they cannot live where we live; they cannot belong to our clubs or afford the restaurants and hotels which we patronize. But these shiny cars are something in which they can take pride: a compensation for their deprivations.

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*Address to the University of Minnesota Graduating Class in Medicine, June 7, 1968.

Then, he added, some women ostentatiously wear expensive mink coats. They or their husbands obviously have money. But they may have little else to be proud of. We should understand and sympathize with them rather than envy or criticize them.

How different it is with physicians. We are fortunate in being able to get true satisfaction from our work and our profession. The physician does not need a Cadillac nor his wife a mink coat to bolster their egos. Emerson wrote, "The greatest reward of a thing well done is to have done it." This is particularly true of the profession which you are about to enter. Your greatest rewards will be your achievements and the services you render, not the financial remuneration you will receive. Your income should and will be adequate to provide a dignified and comfortable living and the opportunities and security your families deserve. Beyond that, money loses its purchasing power for happiness and may well become one's master instead of being one's servant—a liability instead of an asset.

A poll of several hundred practicing physicians were asked their definition of success and it revealed first and foremost: good doctor-patient relationships, and second: good education and training. Other prerequisites for success were: honesty and integrity, willingness to work hard, availability to patients, high quality of work, judgment and skill in diagnosis and treatment, keeping abreast of medical progress, getting along with colleagues and having their respect, intelligence, unselfish dedication to medicine, drive for self-improvement, community welfare and civic responsibilities, and finally, as least important, financial success.

In these days of insecurity and avariciousness there is a temptation for physicians to follow what seems to be the pattern for labor and for business: to get all one can out of the public, particularly if the Government pays the bill. Commercialism and excessive professional fees bring public disfavor to our profession. The primary service that is expected of a physician is to prevent or to cure disease and, if that is not possible, to relieve suffering and to provide comfort.

It was physicians who developed and then persuaded the public to utilize preventive measures that have virtually eliminated smallpox, diphtheria, tetanus, poliomyelitis, typhoid fever, cholera, malaria, yellow fever and other diseases. Similar possibilities for distinguished service exist today and will continue in the future.

An example, with which I have been greatly concerned in recent years, is the problem of cigarette smoking. The Surgeon General of the United States Public Health Service has said that it is the major preventable cause of illness, disability and premature death in this country. It is responsible for an estimated 70,000 annual deaths from cancer; 145,000 from coronary heart disease; 43,000 from strokes and other cardiovascular diseases, and 44,000 from chronic bronchitis, emphysema and other causes—300,000 in all.

A recent survey by the California State Medical Association indicated that 96 percent of physicians consider cigarette smoking a serious health hazard but that only 38 percent advise their patients not to smoke unless they have symptoms attributable to smoking. Dr. Howard has stated that, "A teacher who influences children not to smoke cigarettes can do more to reduce deaths and disability from lung cancer and emphysema than the most skilled surgeons and physicians who care for the patients who develop these diseases."

As to the years ahead only a crystal gazer would attempt to prophesy; but the need for well trained and dedicated physicians was never greater than today and the advances in medical, biological, chemical, physical and social science research are opening vistas of further progress that over the next half century may well surpass the brilliant achievements of the past.

I congratulate you and I envy you the privilege of participating in the wonderful opportunities that lie ahead as you face the challenges of our changing world. God-speed to you all.

It's the Law

Cost of Kidney Transplant Deductible by Donee

A kidney transplant patient, who paid the kidney donor's plane fare and entire hospital bill, was allowed to deduct these costs as medical expenses, the Internal Revenue Service ruled.

The donor traveled from a distant city and entered the hospital as a patient for the purpose of donating the kidney. The kidney recipient paid all transportation, surgical and hospital expenses incurred.

IRS Rev. Rul. 68-452, I.R.B. 1968-34, 16.
The Citation, Vol 17, No. 12, October 1, 1968.

Shakespeare: Medicine

Miscellaneous

"Here comes lean Jack, here comes bare bones. How long
is't ago, Jack, since thou sawest thy own knee?"
"My own knee? when I was about thy years, Hal, I was not
an eagle's talon in the waist; I could have crept into
any alderman's thumb-ring: a plague of sighing and grief!
it blows a man up like a bladder."
"The king himself is to be feared as the lion. Dost
thou think I'll fear thee as I fear thy father? Nay,
an I do, I pray God, my girdle break!"
"O, if it should, how would thy guts fall about thy knees!"*

---

*Falstaff and Prince Hal in Henry IV, Part II: III, 2,3.

Classified Advertisements

Classified advertising rates are twenty (20) cents a word; minimum monthly charge $5.00; key number, fifty (50) cents additional.

Replies to advertisements with key numbers should be mailed in care of Minnesota Medicine, 375 Jackson, St. Paul, Minn. 55101.

WANTED: Young physician for association leading to partnership with four well established General Practitioners in fast growing suburb of St. Paul. Excellent clinic facilities in nearly new, partnership owned, well equipped, medical center building. Write: Minnesota Medicine-421, 375 Jackson, St. Paul 55101.

WANTED. General practitioner wanted to join three-man group in a fast-growing area just 30 minutes south of the Twin Cities. You will practice in a new clinic, hospital and nursing home. A complete resume of facilities, practice and area is available. Contact M. H. Hunter, M.D., River's Edge Medical Clinic, Farmington, Minnesota. Telephone 612-463-7181.

OXBORO MEDICAL CLINIC BUILDING (only) for sale in Bloomington, Minnesota's third largest city. Earn attractive return while current lease expires in four years. Clinic comfortably houses 11 doctors, each with 3½ examination rooms. Central air conditioning, adequate parking, and much more. Contact Towle Real Estate Co., 333-2445, Area Code 612. James R. Bingham.

DIRECTOR OF HOUSE SERVICE—An ideal position for someone in family practice who wants a less strenuous life in a stimulating medical environment. Excellent annual fee, plus fringe benefits. Located in Minneapolis, known nationally as an ideal city for family living. Every possible professional, educational, cultural and recreational opportunity. Teams in all major league sports. Write of your interest and come for an expense-paid visit. Write: Minnesota Medicine-422, 375 Jackson, St. Paul 55101.

OB-GYN—Join group of 4 GP's. Immediate work load. Time off assured. Early partnership opportunity. Well equipped clinic, established in 1962, recently expanded, in growing community of 7,000, 30 minutes from downtown Minneapolis-St. Paul. Fully accredited 116 bed hospital in community. Call or write J. E. Ponterio, M.D. (612) 445-1305. Shakopee Medical Center, Shakopee, Minnesota.

GENERAL SURGEON, board certified or eligible wanted for 5 man group practice community sponsored prepayment plan in Northeastern Minnesota area of 14,000 located on Lake Superior 20 miles from Duluth. Anesthesia by physicians. No general practice. Accredited hospital with radiologist and pathologist services next door to modern clinic. Good schools with swimming pool and indoor ice arena, golf, hunting, fishing. Liberal salary, full partnership 6 months. Write Medical Director, Community Clinic, Two Harbors, Minnesota.

CANOE TRIPS—Complete relaxation in the Quetico-Superior Wilderness. Cruise, fish and explore, or base camp on remote lakes. Paddle, motor or fly in. Bring your family—return home completely rested. Cost only $9.00 per diem, $7.00 under 12. Write: Bill Rom, Dept. MM, Canoe Country Outfitters, Ely, Minnesota.

GENERAL PRACTITIONER urgently needed with two man partnership in Northern Minnesota County Seat Community has modern accredited hospital, stable industry, fine schools and excellent hunting and fishing. Contact Administrator, Roseau Area Hospital, Roseau, Minnesota. Telephone No. 218-463-2500.

EXCELLENT OPPORTUNITY for one or two general practitioners. Deer River, Minnesota will be needing one or possibly two physicians by June 1, 1969. The present partnership has an extremely busy practice with higher than average income. An equipped ten room clinic in the hospital is available. For further information contact David McClure, Administrator, Community Memorial, Deer River, Minn. Call collect (218)-246-8245 weekdays or 246-8274 evenings or weekends.

WANTED: Young General Practitioner to join 5 man general practice group. Services of General Surgeon and Radiologist immediately available. College town serving population of 22,000, 30 miles from Twin Cities. Contact Roland M. Hammer, M.D., River Falls Medical Clinic, River Falls, Wisconsin. Phone 425-5322.

WANTED: G.P. to join clinic serving population area of 12,000. City has new hospital, new clinic building, two nursing homes, new Jr-Sr high school, new swimming pool, rich farming area. Fishing and hunting nearby; metropolitan city close by. Salary open and partnership if interested. Write Minnesota Medicine-423; 375 Jackson, St. Paul 55101.

GENERAL PRACTITIONER WANTED to join well-established three man group in Twin City area. Starting salary $20,000.00 to $25,000.00 range with opportunity for early partnership; or, will negotiate. Write: Minnesota Medicine-424, 375 Jackson, St. Paul 55101.

TEN MAN MULTISPECIALTY group needs an ophthalmologist and another pediatrician. New clinic building, complete laboratory and x-ray facilities. 180 bed modern hospital across street from clinic. Early share-holder status. Salary open. Write or call the Lenont-Peterson Clinic, Ltd., C. A. Tietz, M.D., area code 218, 741-4292, Virginia, Minnesota 55792.

LONG LAKE NEEDS DOCTOR. Professional Bldg. for sale or rent. Has waiting room with reception counter, two toilets, lab-darkroom, large X-ray room plus five other rooms. Picker 100-100 Century available. Sublease area has large room and toilet, suitable for dentist or other Professional with shared waiting room. All new modern interior. Wide open; no Doctor in town. Jay R. Kallestad. A.C. 612-920-7687.

BENSON & ASSOCIATES: Business & Professional Collection Specialists. No charge if no collection made. Ph.: 888-2242, 8601 Nicollet Ave., Bloomington, Minn.

Continued on page 704.

Meetings and Announcements

Knowledge comes, but wisdom lingers.—Tennyson

APRIL

Scott-Carver County Medical Society
Regular Meeting, Wagner's Supper Club, Jordan, 6:30 P.M., April 1.
Brown County Medical Society
Spring Meeting, Orchid Inn, Sleepy Eye, 7 P.M., April 8.
Winona County Medical Society
Regular Quarterly Meeting, Williams Hotel, 7 P.M., April 8.
Minnesota Academy of General Practice
House of Delegates—Hotel Radisson, 1:30 P.M., April 8.
Spring Refresher—Hotel Radisson, 9:00 A.M.-5:00 P.M., April 9-10.
Minnesota Academy of Medicine, Town & Country Club, 6:00 P.M., April 9, St. Paul.
Minnesota Academy of Ophthalmology & Otolaryngology
Regular Meeting, Minneapolis Athletic Club, Dinner, 7 P.M., Meeting, 8 P.M., April 11.
Blue Earth Valley Medical Society
Regular Meeting, Interlaken Golf Club, Fairmont, 7 P.M., April 16.
McLeod County Medical Society
Regular Meeting, 6:30 P.M., April 17, Location to be announced.
Freeborn County Medical Society
Dinner Meeting, 7 P.M., April 17, Location to be announced.
Stearns-Benton County Medical Society
Regular Meeting, David's (South of St. Cloud on Highway No. 152), 6:30 P.M., April 17.
Twin City Urological Society
Town & Country Club, 6 P.M., April 18.
Waseca County Medical Society
Regular Meeting, Waseca Memorial Hospital, 6:30 P.M., April 28.
Blue Earth County Medical Society Meeting, Century Club, 7 P.M., April 28.

Courses at the University of Minnesota

Proctology

The University of Minnesota will present a continuation course in Proctology from April 21-25, 1969. Through clinical sessions, attention will be specifically devoted toward teaching each registrant the details of proctoscopy. In addition, management of the more commonly encountered proctologic problems will be discussed, as well as the diagnosis and treatment of the most usual anorectal diseases.

Ophthalmology

The University of Minnesota will present a course in Ophthalmology on April 28-29, 1969. This year's course will be concerned with the medical treatment of ocular disease, with emphasis on the treatment of inflammatory ocular diseases and use of newer drugs in ophthalmology. Ample time will be provided for panel discussion of questions by the lecturers. For further information regarding the above courses contact: Lee D. Stauffer, College of Medical Sciences, Box 193 Mayo Building, University of Minnesota, Minneapolis 55455.

New Knowledge in the Diagnosis and Treatment of Rheumatic Diseases

This course is planned for May 9 and 10, and is directed toward the practicing physicians with emphasis on this newer information and its application to the rheumatic problems encountered in every medical practice. Ample time has been left for discussion after each presentation so participants will have the chance to have their questions answered.

The course has been planned by Doctors John G. Mayne and John W. Worthington, Mayo Graduate School of Medicine, and is co-sponsored by the Committee on Rheumatology and Rheumatic Diseases of the Minnesota State Medical Association, and by the Minnesota Chapter of the Arthritis Foundation. The course is offered by the Office of Postgraduate Educational Activities of the College of Medical Sciences, and conducted by the Department of Conferences and Institutes, General Extension Division, University of Minnesota. Tuition is $25.00. Approved A.A.G.P. hours: 11 hours.

Contact: Lee D. Stauffer, College of Medical Sciences, Box 193 Mayo Building, Minneapolis.

Continued from Page 702.

GENERAL PRACTITIONER wanted to join well-established practitioner. New clinic building—90 miles east of St. Paul—city of 14,000. Early partnership with full hospital facilities. Ideal location. L. W. Picotte, M.D.; Chippewa Falls, Wisconsin.

ASSOCIATE urgently needed in busy general practice. Excellent clinic and hospital facilities. Salary open. Partnership after 1 year. Klefstad Clinic, Greenbush, Minn. Call collect: Lloyd H. Klefstad, M.D., Tele. 218—782-5275 or 4725.

INTERNIST: Board certified or eligible. 269-bed General Medical and Surgical Hospital in Michigan's Upper Peninsula. Licensure any state, salary dependent upon background and qualifications. Excellent benefits for retirement, vacations, sick leave, and professional improvements. Non-discrimination in employment. Contact Chief of Staff, VA Hospital, Iron Mountain, Michigan 49801.

NINETEEN-MAN Wisconsin group located in college community of 40,000 with excellent hospital facilities is seeking additional associates in the following areas: (1) Internal Medicine, (2) General Practice, (3) Pediatrics and (4) Orthopedics. For further information please contact D. R. Griffith, M.D., Midelfort Clinic, Eau Claire, Wisconsin 54701.

WANTED: General practitioner to join two young general practitioners in well-established practice in suburban St. Paul. Excellent office space with lab, x-ray, and emergency room. Salary negotiable, with an association leading to early partnership opportunity. Write MINNESOTA MEDICINE 412, 375 Jackson St., St. Paul 55101.

INTERNIST AND GENERAL PRACTITIONER wanted to join a five-man clinic group in Minneapolis. Complete laboratory and X-ray with board roentgenologist. Excellent hospital staff associations. Salary arrangement to start with, early partnership. Write MINNESOTA MEDICINE—289; 375 Jackson, St. Paul, 55101.

THREE MAN group in North West Wisconsin Resort, State Conservation and Retirement Area needs two more physicians adequately to serve their practice. Facilities offered are three-room physician suites, X-ray and lab under AMT technician, RN-only nursing personnel. New accredited thirty-two bed hospital and forty-six bed nursing home. Deer and duck hunting, fishing within five minutes of town. Internist most needed; generalists welcomed. Will meet any reasonable salary request. Partnership after one year. Write: MINNESOTA MEDICINE—365; 375 Jackson St., St. Paul 55101.

EXPANDING EIGHT-MAN CLINIC IN NORTHWESTERN WISCONSIN has immediate openings in General Practice, Internal Medicine and Urology. New clinic building; three accredited hospitals; large branch of the University of Wisconsin; population 33,000. Liberal first year salary, early partnership. Contact Milton Finn, M.D., 3600 Tower Avenue, Superior, Wisconsin 54880. Tel.: 715-392-8111.

GENERAL SURGEON: Board certified or eligible. 269 bed General Medical and Surgical Hospital in Michigan's Upper Peninsula. Licensure any state, salary dependent upon background and qualifications. Excellent benefits for retirement, vacations, sick leave, and professional improvements. Non-discrimination in employment. Contact Chief of Staff, VA Hospital, Iron Mountain, Michigan 49801.

WANTED: G.P. for one year Locum Tenens or permanent practice in a friendly, relaxed, medically progressive community in northern Minnesota. Summer and winter recreation excellent; liberal salary & ample time off. Early partnership if desired. Start July 1, 1969 or sooner if desired. Contact Doctors Brende and McQuoid, Littlefork, Minn. 56653 or call collect 218-278-6651.

GENERAL PRACTITIONER—Join 3 physicians 50 miles from Minneapolis. $1,600.00 to $2,000.00 a month to start—early partnership. Rotating call. 65 bed hospital. Call collect: 612-864-3116. Glencoe Medical Clinic, Glencoe, Minn.

FOR SALE: Clinic—completely equipped—four examining rooms—two consultation offices—business office—large waiting room and storage. Located 50 miles from Minneapolis and St. Paul in town of 900 population. Local hospital equipped for general medicine, major and minor surgery—medicare approved. Price for clinic including large lot for expansion, $25,000. Terms may be arranged if needed. Have practiced with associate for over 25 years. Reason for selling: retirement. Wonderful opportunity for two doctors. Practice unopposed. If interested write MINNESOTA MEDICINE-426, 375 Jackson Street, St. Paul, Minnesota 55101.

GENERALISTS & PSYCHIATRISTS—In accredited progressive 2000 bed mental hospital with approved psychiatric residency training program. Ideal living in active resort community located in Michigan's serene, scenic water-wonderland. Salary $20,880 to $28,480 depending on qualifications. Unparalleled retirement and fringe benefits. Contact M. Duane Sommerness, M.D. Superintendent, Traverse City State Hospital, Traverse City, Michigan 49684. An equal opportunity employer.

INTERNIST—Certified, FACP, endoscopial, available June 1969. Write: Minnesota Medicine-425, 375 Jackson St., St. Paul 55101.

WANTED—Practitioner—Battle Lake, near Fergus Falls, in the heart of Minnesota Lakeland, to share with single-handed practitioner. Hospital facilities. Fully equipped office. Available for immediate occupancy. Duties to be shared equally with present practitioner. PARTNERSHIP or GUARANTEED INCOME, whichever desired. Please call collect: 218-864-5225 (Day), 218-864-8136 (Evening). Will meet in the City, if desired. Battle Lake Medical Center, Battle Lake, Minnesota 56515.

LOCUM TENENS—General practitioner available after July 1969. 15 years experience. Active, successful practice. Excellent qualifications and references. Licensed Minnesota. Twin Cities preferred. Write MINNESOTA MEDICINE-427, 375 Jackson St., St. Paul 55101.

Minnesota Medicine at a Glance

Infarct of the Prostate—*Antolak* Page 591

Infarct of the prostate is a well recognized entity infrequently diagnosed clinically, but discovered at autopsy or pathologically post-T.U.R. It usually causes symptoms of acute urinary retention that are compatible with benign prostatic hypertrophy. The reported case describes an unusual complication in which the infarct obstructed the ureteral orifice, producing a pyohydronephrosis. The method by which the case was successfully managed is reported.

Thymoma with Myopathy—*Souadjian et al.* Page 595

The authors report an interesting case of a lady with very diffuse symptoms centering around muscle weakness. This patient, in addition, was discovered to have a mediastinal mass which, on removal, was found to be a thymoma. Following the removal of the thymoma, the symptoms regressed. This may be the first report of a patient with thymoma and diffuse myopathy whose symptoms and findings decreased following thymectomy.

Steroid Diabetes—*Gharib* Page 669

Relatively short but concise review of difficult subject.

What's New

Attention: All directors of medical education, intern training committees, nursing instructors and public relations committees!

Smith Kline & French Laboratories has just released its new services catalog for 1969-70. This new catalog contains numerous films, periodicals, and pamphlets directed toward the training and education of physicians, nurses and laymen. The scope of these educational services is broad and does not permit summarization. Those interested are invited to obtain a free copy of this catalog by contacting their SK&F representative or by writing to the Services Department E-10, Smith Kline & French Laboratories, 1500 Spring Garden Street, Philadelphia, Pennsylvania 19101.

* * * *

Physicians are hereby alerted to watch for the appearance of Eskavan, a specially designed, mobile theater of medical information sponsored by Smith Kline & French Laboratories. This self-contained and air-conditioned audio-visual "auditorium" is designed in the form of a traveling bus and will visit hospitals. Inside the bus, the physician may watch and listen to various medical films from six to eleven minutes in length with individual headphones permitting several subjects to be presented simultaneously. Watch for this innovation in your hospital parking lot in the future.

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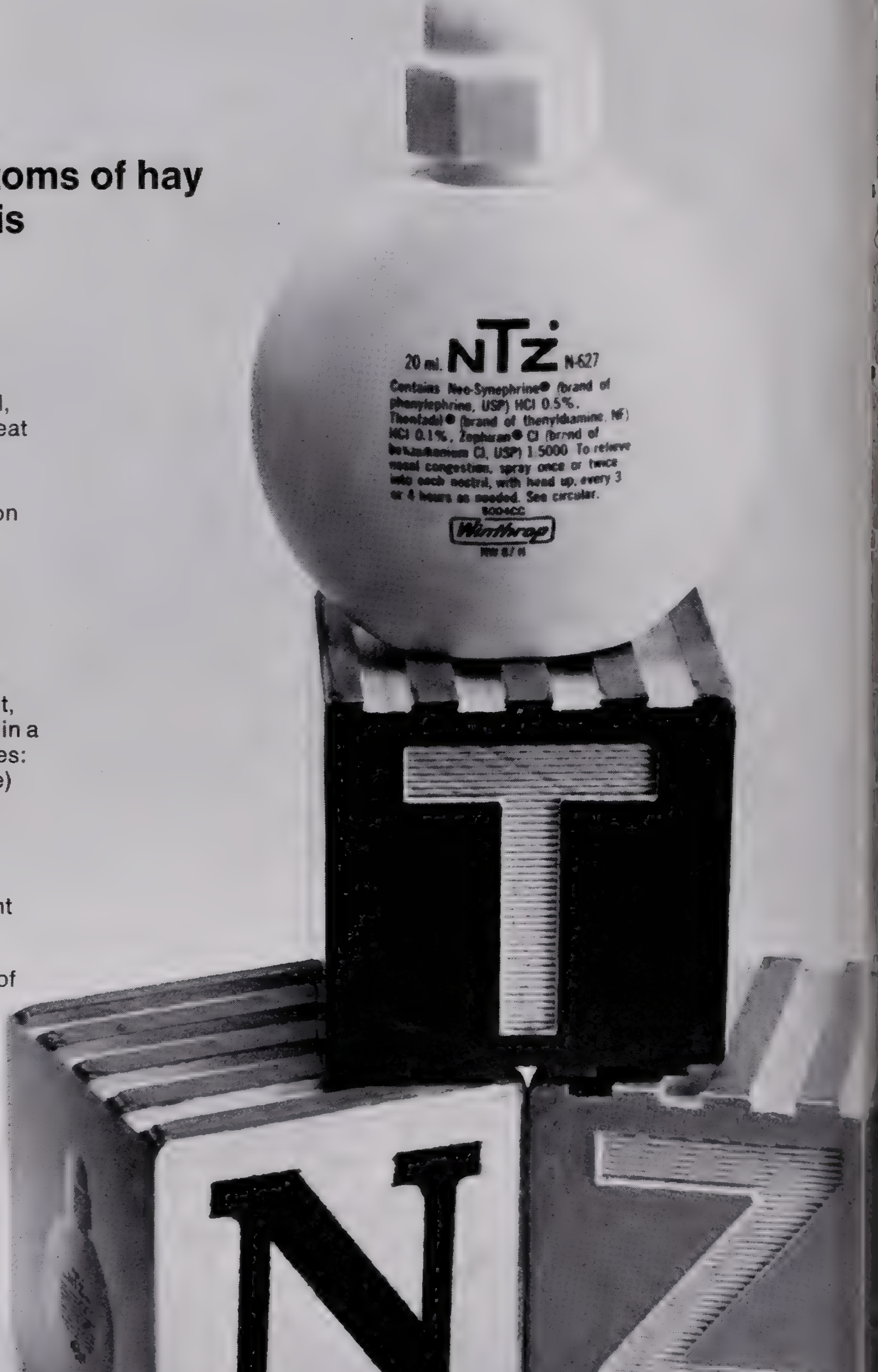
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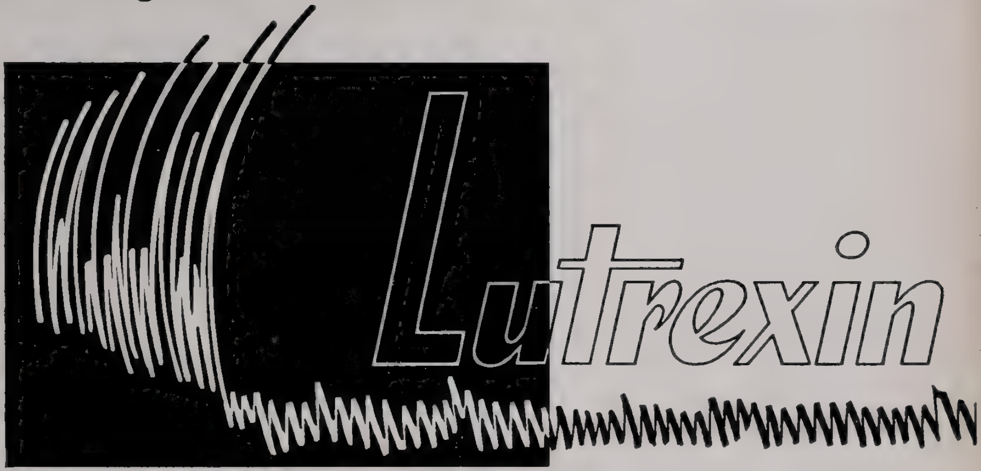

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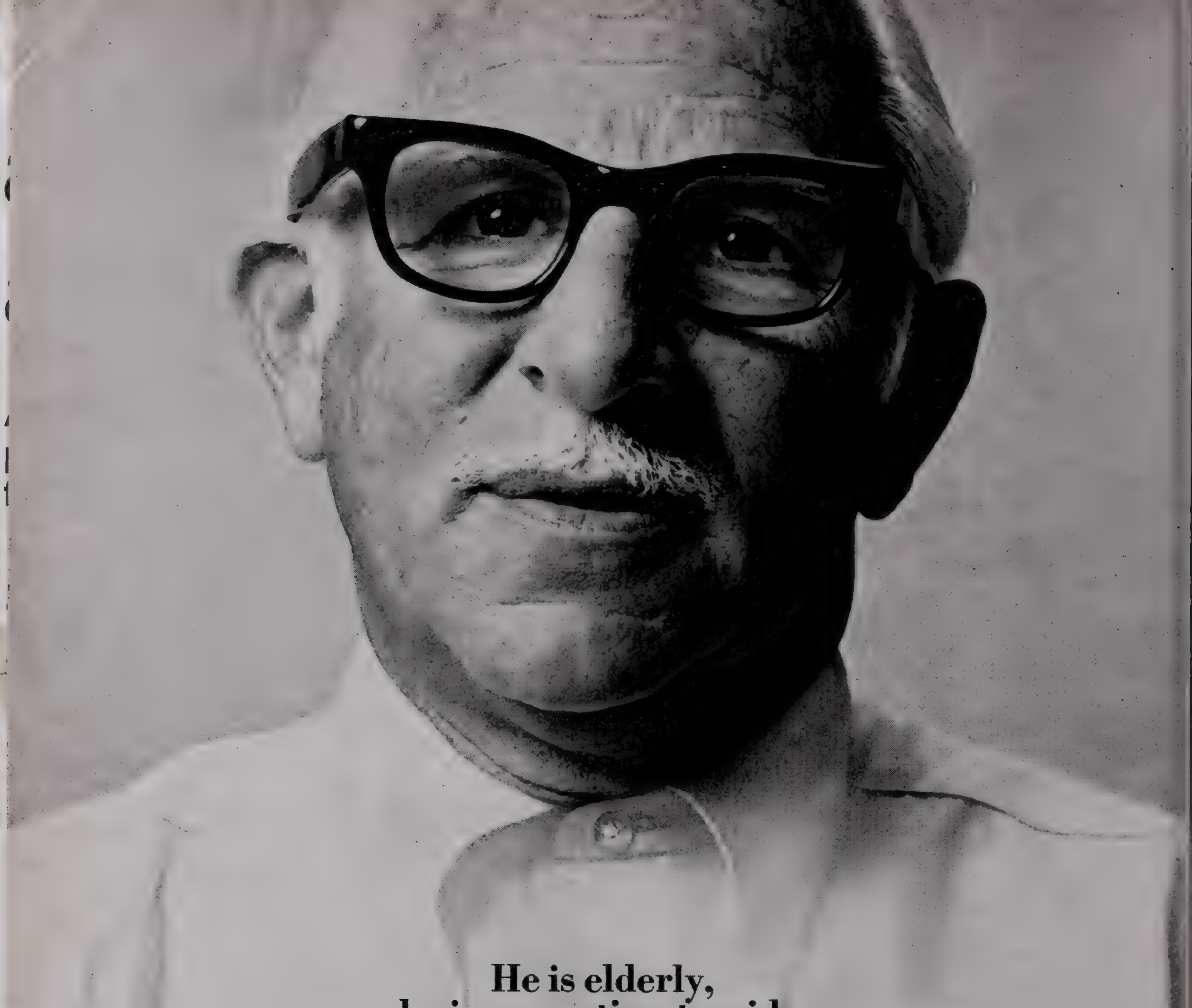

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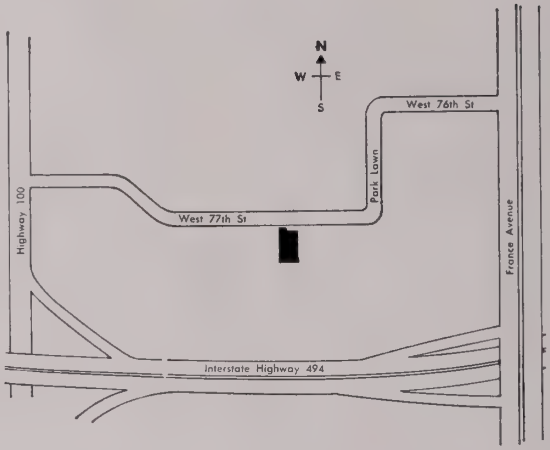

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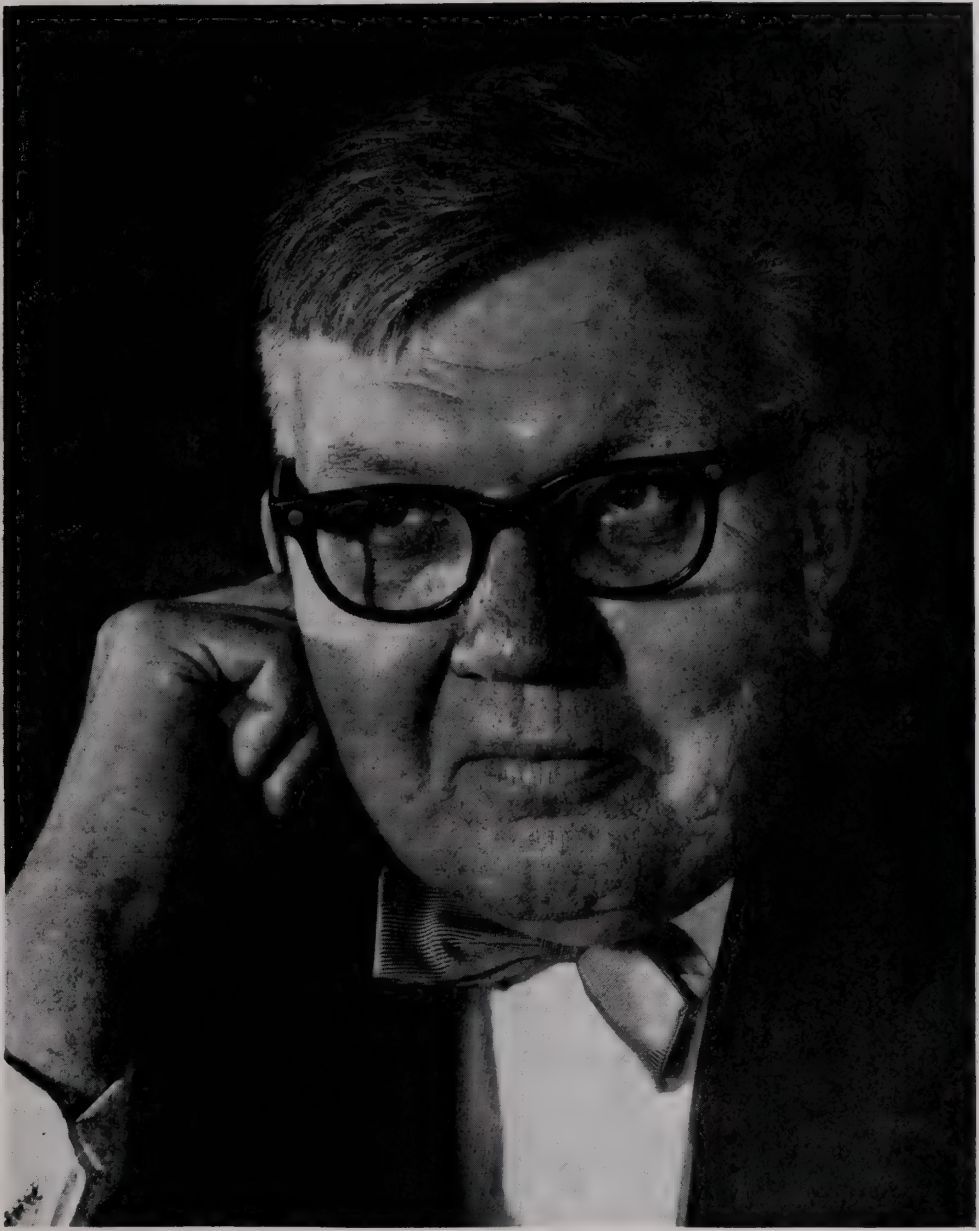

O. L. N. Nelson, M.D.

President

Minnesota State Medical Association

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President's Letter

116th Annual Meeting

As the time for the 116th Annual Meeting of the Minnesota State Medical Association approaches, it behooves us to reappraise this meeting. Though not as catastrophic, our experience parallels that of the surrounding states—steadily declining interest, with resultant fall-off in registrants and commercial exhibitors (who, up to now, have underwritten a good share of the expenses). This is probably an inevitable trend in that as we multiply our splinter groups, we divide our members' loyalties. Of further concern is the possibility that the Internal Revenue Service will regard exhibitors' fees as income and tax us accordingly.

It has been my very good fortune to have the support of a strong and innovative program committee this year and last. In 1968 they developed the "in depth" concept—in 1969 they have added the multiple roundtables approach. They have essayed to draft a format acceptable to and palatable for all. Your response will help to shape future policy.

Many of our members have stated that the Annual Meeting should be devoted to socio-economic matters, leaving scientific programs to the splinter groups. The Annual Refresher Courses of the Minnesota Academy of General Practice and of the Mayo Clinic have been most successful, and they are unquestionably competitive with our meeting. In addition, each specialty group has one or more scientific sessions annually. Attempts to meld these diverse parts into an acceptable whole have thus far failed.

With mixed feelings, I surrender this post after a somewhat longer than usual tenure. I am grateful for the generous and continuing support of the Council and officers of your Society. Thanks to Dr. Carl Rice, who has accepted and embellished recommended changes in the President's Page. As always, Mr. Harold Brunn has been the invaluable aide-de-camp. Finally, without the stimulation and assistance of Miss Elaine Nye, these visits could not have been so enjoyable for me.

So, we change the guard—join me in a hearty welcome to Dr. Delmar Gillespie, your President soon to be.

O. L. N. Nelson, M.D., President
Minnesota State Medical Association

minnesota medicine

STATE MEDICAL ASSOCIATION

Volume 52

Number 5

PRESIDENT'S LETTER 713

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Post - Intubation Granuloma of the Larynx

RICHARD A. SCHLORF, M.D.*
ARNDT J. DUVALL, III, M.D.*
Minneapolis, Minnesota

POST-INTUBATION LARYNGEAL GRANULOMAS have been reported to occur in from one in eight hundred[4] to one in twenty thousand[2] intubations. They are most common in women and have not been previously reported in children.[4,5] A granuloma should be suspected when a patient becomes hoarse, suffers ear pain, or has a persistent cough after translaryngeal intubation. The majority are noted by the eighth week postoperatively.[4] The diagnosis can be confirmed by indirect or direct laryngoscopy.

Case Reports

Case 1

A 32-year-old non-smoking male required surgery for regional ileitis on June 7, 1967. He fared well and was extubated in the Recovery Room following a four-hour operation. The postoperative course was not complicated. Several weeks after surgery he noted the onset of hoarseness. His voice became increasingly breathy.

Indirect laryngoscopy in October, 1967, revealed a red, polypoid, pedunculated mass attached to the posterior portion of the left vocal cord. In December, 1967, under methoxyfluorane (Penthrane) anesthesia using the Zeiss operating microscope, the mass was removed. Postoperatively the patient's voice returned to normal.

Case 2

An eleven-year-old female underwent surgery for pulmonary stenosis. She was intubated for nine hours, six in the operating room and three in the recovery room. Because of increasing pneumonitis and dyspnea, a tracheotomy was performed on the fourth postoperative day. Her respiratory status improved and the tracheotomy tube was removed on the eleventh postoperative day. Recovery was swift and she left the hospital on the fifteenth postoperative day. Twenty days after discharge she developed hoarseness which progressed to a breathy voice and inability to speak above a whisper. In November, 1967, indirect laryngoscopy revealed a mass occluding the glottic chink by fifty per cent. Under general (Penthrane) anesthesia, without intubation, a posteriorly attached subglottic cherry-red mass was removed with a laryngeal biopsy forceps without cautery. Postoperatively the patient's voice returned to normal.

---

*Department of Otolaryngology, University of Minnesota Medical School, Minneapolis.

Granuloma of Larynx

There have been numerous reports in the literature on post-intubation granuloma since the first description by R. J. Clausen in 1932.[1] New and Devine[3] pointed out that it shares many common features with the contact ulcer granuloma. The appearance and histology are similar; the etiology and natural history, dissimilar.

Contact Ulcer Granuloma

The contact ulcer was described by Jackson in 1928 as a chronic ulcer most commonly located on the vocal process of one or, commonly, both vocal cords, with or without granulations. It is caused by vocal cord trauma, and its persistence is thought to be due to anatomical and physiological factors.[10] The granuloma has been described[7] as a complication of the contact ulcer, and is characterized by a smooth, discrete, whitish mass on one or both vocal processes. These growths are much more common in men, particularly "voice users," and tend to recur after removal. The attachment varies from sessile to pedunculated.

Post-intubation Granuloma

In contrast, the post-intubation granuloma is that tumor which arises following intubation and is generally located at, or very close to, the vocal process of the arytenoid cartilage. While this is the most common location, it has been reported on the middle and anterior thirds of the cord and on the subglottic surface.[2] The originally reported lesion was subglottic in location.[1] Posterior commissure granulomas are apparently rare.[9] In Case 2 the granuloma was in this position. In less than 50% of cases both cords are involved.[2,4,5] Holinger found the post-intubation granuloma to be located more often inferior and posterior in the hyaline cartilaginous body in close approximation to the vocal process.

In addition, the post-intubation granuloma is generally larger and broader-based, presenting a more polypoid appearance. Over eighty per cent of the lesions have been reported in women. When surgery is necessary for removal, the recurrence rate of the contact ulcer granuloma is considerable higher than for the post-intubation granuloma.

Etiology

Howland and Lewis[4] state that if the head is in a non-neutral position (extended, turned toward the side and extended) the larynx is in a relatively higher plane with regard to the head, forcing the pressure of the tube posteriorly in the glottic chink.

Size of Glottic Opening

Some appreciation is gained for relative size when we note that the outside diameter of the number 32 uncuffed endotracheal tube is 10.7 mm., while the length of the vocal fold is 23 mm. in adult males and 17-18 mm. in

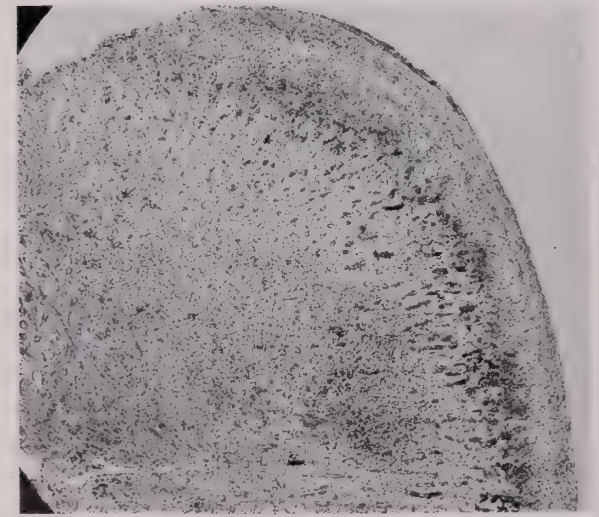

Fig. 1—Granulomatous polyp, Case 1. Fibroblasts, immature collagen fibers and vascular channels with infiltrating polymorphonuclear cells.

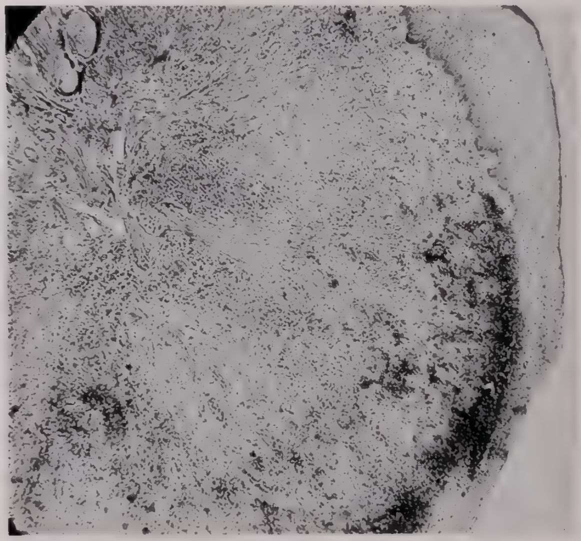

Fig. 2—Case 2. Epithelium partially covers the granulation tissue.

females. The tube can occupy over 50% of the glottic opening in the smaller larynx. The more delicate mucosa of the female larynx probably contributes to its higher incidence; however, the low rate of occurrence in children is not explained by this reasoning. Thyroid operations have been reported to be a major contributor to intubation granulomas, possibly because of the head position required by this operation. Head motion tends to move the tube about in the larynx. A smaller tube may have more freedom to move and thereby cause trauma to the mucosa more easily than a firm-fitting larger tube.

Movement of Larynx

Swallowing movements during light anesthesia increase trauma.[5] The common practice of leaving the endotracheal* tube in place several hours postoperatively while the patient becomes increasingly alert may contribute to mucosal trauma. Prolonged intubation during anesthesia has not increased the incidence of the post-intubation granuloma.[2]

The role of pre-existing infection, allergy, and traumatic intubation is probably secondary to head position in causing granulomas. Applications of antibiotic and steroid medication to the endotracheal tube have not been shown to be of benefit in either decreasing postoperative sore throat or more serious complications.[8] Nor have systemic steroids been found beneficial.

Pathogenesis

These laryngeal tumors are thought to arise from minor, even microscopic, abrasions of the delicate mucosa over the vocal process of the arytenoid cartilage that occur during intubation. The exposed cartilage then becomes infected. This abrasion can be referred to as a "contact ulcer." The ulcer matures to a sessile granuloma as the denuded area becomes covered with granulation tissue in an attempt to cover the exposed cartilage. The lesion becomes an inflammatory polyp, or pyogenic granuloma, through central proliferation. This is generally five to nine millimeters in diameter.[5] If the patient is fortunate, the tumor eventually shrinks as vessels invade it, and organization occurs. Months later these lesions become angiofibromas of the cord and in time may disappear.[6]

Management

The problem of management is complicated by the natural history of the tumor. Early it is characteristically a pyogenic granuloma (chronic non-specific inflammation), greyish in color. In time its size decreases and the color becomes reddish. Later the mass may decrease to an asymptomatic size. Spontaneous auto-amputation has been reported.[1,6]

Rest the Voice

However, the post-intubation granuloma commonly causes troublesome interference with voice production, and difficulty arises when a person depends on his voice for his livelihood. Vocal abuse affects the course of this tumor, and post-intubation voice rest may decrease the incidence. Medical therapy is doomed to fail in a patient unable to cooperate in a program of vocal conservation, hastening the need for surgical intervention. Voice rest after intubation is particularly recommended if signs of laryngeal irritation are present postoperatively.[5]

Surgery

Surgical removal becomes more urgent when the airway is in danger of being obstructed, or when a malignant neoplasm cannot be ruled out. Here excision and pathological study are indicated. In Case 2 the mass was of such a size that any edema in the glottic tissues could easily have caused an airway obstruction.

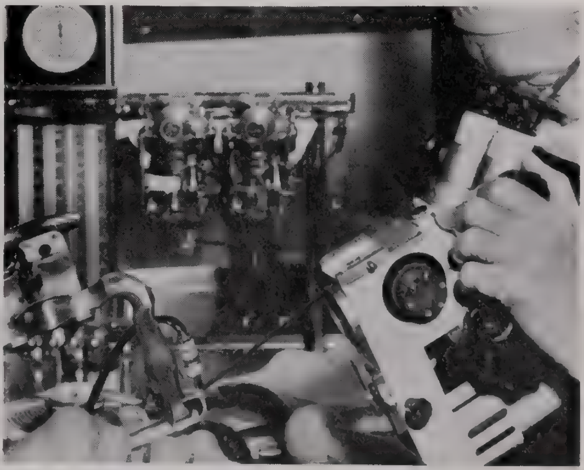

Fig. 3—Posed photograph showing the operating microscope and the laryngoscope in place.

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*See Test Your Word Score Page 759.

When the treatment becomes surgical, these lesions are easily removed by direct laryngoscopy. Lewy suspension laryngoscopy using the Jako laryngoscope provides good visualization. With the intense light and magnification of the Zeiss operating microscope (Figure 3) it is possible to preserve normal tissue. General anesthesia without intubation is recommended to increase visualization, prevent disruption of the mass, and lessen the possibility of recurrence. Methoxyfluorane (Penthrane) has proved valuable because of the prolonged anesthesia possible without an endotracheal tube. Its slow induction and long recovery time are offset by the adequate anesthesia and the relaxation, as well as the exposure gained without the indwelling tube. Postoperative discomfort is minimal and discharge is possible the next day. Voice rest is useful to insure healing.

Removal would best be accomplished in the pedunculated stage after a trial of voice rest and antibiotics. As many as 50% are thought to disappear spontaneously or with medical treatment, including speech therapy. Early removal of a sessile, vascular granuloma has been shown to predispose to recurrence.

Summary

The uncommon occurrence of post-intubation granuloma would suggest that direct visualization, proper-fitting tubes, muscle relaxants, static head positions, and atraumatic intubations are worthwhile. General anesthesia and the operating microscope are recommended for accurate surgical removal, after a trial of medical treatment.

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Humoral Types

Foure humors raigne within our bodies wholly,
And these compared to foure Elements,
The Sanguine, Choler, Flegme, and Melancholy,
The latter two are heavie, dull of sence,
Th'other two are more Iovial, quicke and Iolly.
And may be likened thus without offence,
Like ayre both warme and moist, is Sanguine cleare.
Like fire doth Choler hot and drie appeare.
Like water cold and moist is Flegmatique,
The Melancholy cold, drie earth is like.

—**Regimen Sanitatis Salerni**

Editor's note: The school classifies men into four types, each type combining in its nature two of the four universal elements: fire, air, water, earth. Thus the sanguine type is warm and moist (fire and air); the choleric type is warm and dry (fire and earth); the flegmatic type is cold and moist (water and air); and the melancholy type is cold and dry (water and earth).

Hepatitis in Infectious Mononucleosis*

GEORGE KITZMILLER, M.D.†
Minneapolis, Minnesota

INFECTIOUS MONONUCLEOSIS commonly causes biochemical evidence of liver involvement[1-7]. There is often histologic evidence of a hepatitis[8,9]. Persistent abnormalities in liver function tests have been noted[10], and cirrhosis following infectious mononucleosis has been reported[11]. This monograph concerns serial serum glutamic-oxalacetic acid transaminase, alkaline phosphatase, and total bilirubin determinations in a group of patients with infectious mononucleosis, to correlate the liver function abnormalities with the clinical course and to note the duration of the abnormalities.

Materials and Methods

Seventy-five cases of infectious mononucleosis from the Naval Hospital, San Diego, California, from October, 1967, to June, 1968, compose the study group. All patients were hospitalized until their symptoms, fever, and splenomegaly subsided, and the serum glutamic-oxalacetic acid transaminase returned to normal. There were 74 males and one female, and their ages ranged from 16 to 30 years. Seventy-six per cent complained of a sore throat; 67%, of malaise; none was asymptomatic. Forty-four per cent had an exudative pharyngitis; 82%, posterior cervical lymphadenopathy; 48%, splenomegaly, and 70%, an oral temperature greater than 100 degrees F. Ninety-four per cent had more than 50% mononuclear forms in their peripheral blood smear and 94% had heterophile titers greater than 1:28 after guinea pig kidney absorption[12]. Serum glutamic-oxalacetic acid transaminase, alkaline phosphatase, and total bilirubin determinations were made at weekly intervals. All determinations were made using the 12-channel Technicon Auto-Analyzer, and the values were considered abnormal if the serum glutamic-oxalacetic acid transaminase exceeded 55 Karmen Units/100 ml, the alkaline phosphatase exceeded 18 King Armstrong Units/100 ml, or the total bilirubin exceeded 1.2 mg/100 ml. Maximal elevations while under observation are reported.

---

*Work done at Naval Hospital San Diego, California.

†Director, Gastroenterology Division, Department of Internal Medicine, Hennepin County General Hospital, Minneapolis.

Results

Incidence and Degree of Hepatic Dysfunction

Seventeen patients had hyperbilirubinemia. All of these had elevated serum glutamic-oxalacetic acid transaminase values, and 13 had associated elevated alkaline phosphatase values (Table 1). Twenty-one patients had elevated serum glutamic-oxalacetic acid transaminase and alkaline phosphatase values with normal total bilirubin values (Table 2), and 23 had elevated serum glutamic-oxalacetic acid transaminase values only (Table 3). Only one patient had an elevated alkaline phosphatase value with normal serum glutamic-oxalacetic acid transaminase and total bilirubin values. Thirteen patients had no evidence of hepatic dysfunction noted by these studies (Table 4).

TABLE 1

Patients with Total Bilirubin > 1.2 mg/100 ml

Case #	Heterophil*	SGOT	Alkaline Phos-phatase	Total Bilirubin
40	1:896	>360	>50	1.7
18	+**	350	32	1.3
33	1:224	260	36	2.5
17	1:14	>250	>50	>10
16	1:1792	>250	40	3.5
74	1:896	>250	27	2.3
2	+	>250	28	3.5
69	1:3584	>250	29	1.6
21	1:448	230	11	1.4
8	1:112	185	18	2.0
14	1:1792	185	10	3.6
45	1:896	165	42	4.8
12	1:224	155	27	2.0
59	1:448	145	20	1.3
55	1:896	120	12	2.0
22	1:112	110	30	3.2
5	+	110	22	2.0

*Maximal value after guinea pig kidney absorption.

**+ indicates those cases where a heterophil titer was not done, but which had a positive slide test for infectious mononucleosis.

Correlation with the Clinical Course

When patients who had no evidence of hepatic dysfunction were compared with those who had hyperbilirubinemia, there was no difference in the length of the prodromal* period or the degree of lymphadenopathy or splenomegaly. The patients with hyperbilirubinemia, however, had a more severe clinical illness. They were febrile for an average of five days, and those without hepatic dysfunction for an average of two days. Prednisone was used to relieve severe toxic symptoms of fever, prostration, and inability to take nourishment. Twelve patients had symptoms this severe, and all of these had biochemical evidence of hepatic dysfunction. None of those without evidence of hepatic dysfunction required this treatment.

Duration of Hepatic Dysfunction

The serum glutamic-oxalacetic acid transaminase and total bilirubin returned to normal in most cases within two weeks; and no patients had abnormalities of these values beyond five weeks after their hospital admission. The alkaline phosphatase had not returned to normal in six cases prior to discharge. There were no cases of relapse or chronic hepatitis in this series.

Discussion

Infectious mononucleosis produced hepatitis in 83% of the patients in this series; the degree of hepatic dysfunction appears to correlate with the severity of the clinical illness. The results of this series are compared in Table 5 with those previously reported. These data indicate that, excluding the bromsulphalein excretion test, the serum glutamic-oxalacetic acid transaminase is the most sensitive indicator of hepatic involvement; and that the abnormalities of the alkaline phosphatase and total bilirubin, when they occur, are associated with serum glutamic-oxalacetic acid transaminase elevations. The hyperbilirubinemia receded promptly in those cases with elevations. The serum glutamic-oxalacetic acid transaminase returned to normal in most cases within two weeks after hospital admission; none were abnormal five weeks following hospitalization. There were no fatalities.

---

*See Test Your Word Score Page 759.

TABLE 2

Patients with Elevated Alkaline Phosphatase and Normal Total Bilirubin

Case #	Heterophil	SGOT	Alkaline Phos-phatase	Total Bilirubin
65	1:896	>250	45	1.1
19	1:448	>250	35	0.9
75	1:1792	>250	19	1.2
31	1:28	>250	23	0.5
3	1:112	210	19	0.8
32	1:112	100	29	0.7
48	1:3584	190	26	0.6
34	1:112	180	24	0.5
29	1:28	175	23	0.6
23	1:1792	165	24	0.7
49	1:896	160	36	1 2
70	1:1792	145	27	0.8
20	1:1792	144	20	0.6
6	1:1792	140	20	0.9
68	1:1792	130	31	0.7
66	1:896	120	>50	1.2
26	1:56	115	25	0.6
42	1:112	100	22	1.1
9	1:28	85	23	0.6
47	1:224	80	25	0.5
54	1:896	75	23	0.7
44	1:448	40	30	0.5

TABLE 3

Patients with Elevated Serum Glutamic-Oxalacetic Acid Transaminase and Normal Alkaline Phosphatase and Total Bilirubin

Case #	Heterophil	SGOT	Alkaline Phosphatase	Total Bilirubin
62	1:448	230	9	0.5
53	1:224	215	12	1 2
60	1:112	175	9	0.7
72	1:3584	175	17	0.7
57	1:56	160	10	0.8
46	1:56	135	15	0.4
28	1:112	135	10	0.7
27	1:448	120	9	0.7
37	1:448	115	14	0.5
38	1:112	110	12	0.5
39	1:448	95	14	0.4
24	1:14	90	12	1.1
1	1:224	85	12	0.7
51	1:896	80	14	0.7
73	1:3584	75	10	0.5
64	1:896	70	10	0.5
63	1:224	70	10	1.2
35	1:56	70	15	0.6
61	1:112	70	9	1.0
71	1:448	70	12	0.6
58	1:448	65	10	0.8
36	1:112	60	13	0.6
15	1:56	60	12	0 8

TABLE 4

Patients with Normal Liver Function Tests

Case #	Heterophil	SGOT	Alkaline Phosphatase	Total Bilirubin
4	56	30	9	0.5
7	224	20	9	0.7
10	56	45	14	1.2
11	448	20	9	0.3
13	224	40	14	0.8
25	224	30	12	0.6
30	112	40	9	0.5
41	448	35	14	0.6
43	896	40	10	0.6
50	896	50	10	1.0
52	448	50	12	0.4
56	896	50	10	0.6
67	448	40	10	0.5

TABLE 5

Series	BSP	SGOT	Alkaline Phosphatase	Total Bilirubin
Present Series		62 (75)*	35 (75)	17 (75)
Finkel[13]		71 (91)	116 (152)	35 (166)
Rosalki[5]		16 (23)	9 (23)	3 (22)
Rennie[4]		22 (32)	14 (30)	3 (25)
Gelb[7]		39 (47)	35 (43)	21 (49)
Kilpatrick[9]	9 (19)		7 (18)	1 (15)
Bennett[10]	41 (90)		50 (90)	30 (90)
Peterson[3]	19 (33)		9 (12)	12 (40)
Cohn[1]	15 (15)		8 (8)	0 (15)
Barondess[6]			64 (73)	
Schultz[14]	54 (68)		9 (25)	11 (82)

*The numbers indicate the number of cases that had abnormalities; the numbers in parentheses indicate the total number of cases in which the test was performed.

Infectious mononucleosis causes some degree of fatty change and a mononuclear round-cell infiltration of the lobular sinusoids of the liver. There is some cellular necrosis, but widespread parenchymal cell damage, loss of lobular architecture, and stromal collapse have not been noted.[8,9] None of the seventy-five patients had liver biopsies.

Persistent abnormalities of the thymol turbidity and cephalin-cholesterol flocculation tests and bromsulphalein excretion have been noted on occasion[10], but conclusive evidence of a chronic active hepatitis following infectious mononucleosis has not been reported. From this series in which patients were confined to a hospital ward and treated symptomatically, it appears that the hepatitis is of a benign nature. Most patients showed a prompt resolution of their symptoms and hepatic dysfunction within two weeks. When they were discharged from the ward, complaints of asthenia were not significant. Since most patients were symptomatic for no more than two weeks prior to hospitalization, the clinically significant disease process is over within one month in most cases.

Summary

Seventy-five consecutive cases of infectious mononucleosis, studied for liver involvement, revealed that 83 per cent had evidence of hepatitis. The degree of involvement appeared to correlate with the severity of the clinical illness. The hepatitis appeared to be benign and resolved within one month after the onset of the illness in most cases. No cases of chronic hepatitis developed. The serum glutamic-oxalacetic acid transaminase was the most sensitive indicator of hepatitis.

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The Frontier Granny

The fountainhead of folk medicine on the westering frontier was the granny, who grew in reputation with each wrinkle on her face as well as each cure she effected. Elderly Dr. R. T. Whiteman of Cambridge, Idaho, found the granny still practicing in his town when he was a young physician.

"Many a granny has used a mold scraped from cheese as an application to open sores," Dr. Whiteman told me. "She got results, but she didn't know why. Today we derive penicillin from a certain type of mold. Some grannies applied wet tea leaves to a fresh burn, but modern medicine has substituted tannic acid solution which is the active principle of tea leaves."*

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*Richard Dunlop: Doctors of the American Frontier, 1965.

Propranolol in Angina Pectoris

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Propranolol (Inderal®), a beta-adrenergic blocking agent, has been found to be effective in the treatment of angina pectoris.[1,2,3,4] Since January 1968, six patients with intractable angina have been referred to this institution for consideration of bilateral internal mammary artery implantation. Before such a decision was made each patient was given a trial of propranolol and each had a favorable result. It is the purpose of this paper to review our experience with the use of propranolol in angina pectoris, to discuss the physiology of the drug, to review the current therapy for angina pectoris, and to report three deaths with the use of intravenous propranolol (Table).

Case Reports

Case 1

This 51-year-old male was admitted to the Veterans Hospital with a three-year history of recurrent angina on exertion and at rest, currently refractive to nitroglycerin and long-acting nitrates.

Examination

B.P. 124/90, cholesterol 388, FBS 106; electrocardiogram showed nonspecific ST-T changes; cardiac cine revealed left coronary artery calcification with left ventricular enlargement.

Course

Following propranolol 160 mg/D the patient demonstrated a decrease in nitroglycerin requirement, an increase in exercise tolerance and in a sense of well being. Duration of follow-up has been four months.

Case 2

This 42-year-old male was admitted to the Veterans Hospital with a 10-month history of angina on exertion and at rest currently—refractive to nitroglycerin.

Examination

B.P. 135/80, cholesterol 254, FBS 92; electrocardiogram showed T wave changes of ischemia; cardiac cine revealed left and right coronary artery calcification.

Course

Following propranolol 80 mg/D this patient, who had previously been diagnosed as type IV Fredrickson's hyperlipoproteinemia, demonstrated a decrease in nitroglycerin requirement, an increase in exercise tolerance and in a sense of well being. Duration of follow-up has been one month.

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Case 3

This 59-year-old male was admitted to the Veterans Hospital with an eight-year history of angina on exertion and at rest. A past history of three documented myocardial infarctions was obtained.

Examination

B.P. 110/70, cholesterol 393, FBS 97; electrocardiogram showed evidence of old inferior infarction and nonspecific ST-T changes; cardiac cine revealed left coronary artery calcification.

Course

Following propranolol 120 mg/D the patient demonstrated a decrease in nitroglycerin requirement, an increase in exercise tolerance, an improvement in the electrocardiogram, and an increased sense of well being. Duration of follow-up has been three months.

Case 4

This 77-year-old male was admitted to the Veterans Hospital with a three-month history of angina on exertion and at rest not improved by nitroglycerin.

Examination

B.P. 170/70, cholesterol 207, FBS 85; electrocardiogram showed PVC's and nonspecific ST-T changes; cardiac cine revealed left coronary artery calcification.

Course

Following propranolol 80 mg/D the patient demonstrated a decrease in nitroglycerin requirement, an increase in exercise tolerance, an improvement in the electrocardiogram, and an increased sense of well being. Duration of follow-up has been one month.

Case 5

This 59-year-old male was admitted to the Veterans Hospital with a three-month history of angina on exertion and at rest not improved with nitroglycerin.

Examination

B.P. 130/70, cholesterol 276, FBS 141, (abnormal G.T.T.), electrocardiogram showed ST-T changes compatible with subendocardiac ischemia; cardiac cine revealed left coronary artery calcification and left ventricular enlargement.

Course

Following propranolol 120 mg/D the patient demonstrated a decrease in nitroglycerin requirement, an increase in exercise tolerance, an improvement in electrocardiogram, and an increased sense of well being. Duration of follow-up has been three months.

Case 6

This 77-year-old male was admitted to the Veterans Hospital with a three-year history of angina on exertion and at rest not controlled by nitroglycerin or improved by long-acting nitrates.

Examination

B.P. 140/76, cholesterol 330, FBS 165 (diabetic, 1965); electrocardiogram showed nonspecific ST-T changes; cardiac cine revealed left coronary artery calcification.

Course

Following propranolol 120 mg/D there was a decrease in nitroglycerin requirement, an increase in exercise tolerance, and an increased sense of well being. Duration of follow-up has been one month.

Our therapeutic approach to the treatment of intractable angina pectoris with propranolol is to begin with 40 mg/day in four divided doses, increasing every three days by 40 mg until 280 mg/day has been attained. If at this level the patient has not demonstrated improvement he is considered a therapeutic failure and consideration is then given for internal mammary artery implantation for control of angina pectoris.

Discussion

In 1964 propranolol, a beta-adrenergic* agent, was released for clinical investigation.[5,6] A related compound, pronetholol was removed from investigative use after it was shown to produce thymic tumor in mice in 1962.

Physiology

The beta-adrenergic receptors in the myocardium mediate the positive ionotropic effects of the sympathetic nervous system and circulating catecholamines, their main response being to stimulate heart rate and contractility. Besides these actions the sympathetic nervous system has effects on vascular and visceral smooth muscle and on the metabolism of fat and carbohydrate. The two principal mediators of sympathetic nerve stimulation are noradrenaline released from the sympathetic nerve endings and epinephrine released from the adrenal medulla. Beta receptors are inhibitory to bronchial muscle and to vascular tone in skeletal muscle but stimulate the heart, resulting in an increased rate, accelerated A-V conduction, and improved contractility. Beta adrenergic blockade by propranolol causes a reduction in heart rate at rest, after exercise, and following excitement, accompanied by a fall in cardiac output and myocardial oxygen consumption.[7,8] Alpha-adrenergic receptors mediate stimulator response, notably vasoconstriction in skin, kidney and other viscera, and dilatation of the pupil. An alpha-adrenergic blocker (phentolamine) occupies the receptor site and prevents the action of natural or synthetic amines at that site, as in the treatment for pheochromocytoma.

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*See Test Your Word Score Page 759.

Review of Literature

Wolfson[9] found 30 of 37 patients with angina pectoris improved while on propranolol as judged by an increase in exercise tolerance, at least a 50% decrease in the number of anginal episodes, complete cessation of pain from nocturnal and post-prandial angina and a reduction of at least 50% in the number of nitroglycerin tablets needed to relieve pain. The patients were followed from six to 15 months.

Furberg[10] studied 14 patients for a period of two weeks, nine of whom were considered improved, requiring less nitroglycerin, and showing increased exercise tolerance.

In a double-blind crossover study involving 49 patients, Grant[11] found that propranolol in doses up to 240 mg/day relieved angina pectoris.

Gianelly,[12] also in a double blind study, found that propranolol produced clinical improvement in 15 of 19 patients with angina pectoris, as manifested by a reduction in the number of pain episodes, decreased nitroglycerin consump-

TABLE

	Case 1, Age 51	Case 2, Age 42	Case 3, Age 59	Case 4, Age 77	Case 5, Age 59	Case 6, Age 77
Angina History	3-yr. history of recurrent angina with 1 flt exertion & angina at rest; not improved by long-acting nitrates.	M.I. 1967 with 10-mo. history of angina with minimal exercise & at rest; not improved by long-acting nitrates.	8-yr. history of angina with 2-block exertion & at rest; 3 previous M.I. s; CVA in 1967.	3-mo. history of exertional angina & angina at rest.	3-mo. history of angina & angina at rest.	3-yr. history exertional angina & angina at rest; not improved by long-acting nitrates.
Lab Data	B.P. 124/90. Cholesterol 338. FBS 106.	B.P. 135/80. Cholesterol* 254. FBS 92.	B.P. 110/70. Cholesterol 393. FBS 97.	B.P. 170/70. Cholesterol 207. FBS 85.	B.P. 130/70. Cholesterol 276. FBS 141. (Abnormal G.T.T.)	B.P. 140/76 Cholesterol 330. FBS 165. (Diabetic 1965)
Electrocardiogram before Propranolol	Abnormal ECG. Nonspecific ST-T changes of dig. and/or ischemia.	Abnormal ECG. T-wave changes of ischemia	Abnormal ECG. Old inferior infarct. ST-T changes of dig. and/or ischemia.	Abnormal ECG. PVC's & ST-T changes of dig. and/or ischemia.	Abnormal ECG. Subendocardial infarct. ST-T changes.	Abnormal ECG. Nonspecific ST-T changes.
Cardiac Cine	Lt. coronary artery calcification. Lt. ventricular enlargement.	Lt. & rt. coronary artery calcification.	Lt. coronary artery calcification.	Lt. coronary artery calcification.	Lt. coronary artery calcification. Lt. ventricular enlargement.	Lt. coronary calcification.
Therapy	Propranolol 160 mg/day; digoxin 0.25 mg/day; Coumadin 5 mg.	Propranolol 80 mg/day; Isordril 5 mg q.i.d.; Atromid-S 500 mg q.i.d.	Propranolol 120 mg/day; dicumarol.	Propranolol 80 mg/day; Isordril 5 mg q.i.d.	Propranolol 120 mg/day; Peritrate 20 mg q.i d.; Coumadin 5 mg/day.	Propranolol 120 mg/day.
Duration of Follow-Up	4 months	1 month	3 months	1 month	3 months	1 month
Type of Improvement	Decrease NTG requirement. Symptomatic improvement. Increased exercise tolerance. ECG unchanged significantly.	Decrease NTG requirement. Symptomatic improvement. Increased exercise tolerance. ECG unchanged significantly.	Symptomatic improvement; increased exercise tolerance. ECG improved	Symptomatic improvement. Increased exercise tolerance. ECG improved.	Decreased NTG requirement. Symptomatic improvement. Increased exercise tolerance. ECG unchanged	Decreased NTG requirement. Symptomatic improvement. Increased exercise tolerance. ECG unchanged significantly.

*Fredrickson Type IV

tion, and increased exercise tolerance as measured by a treadmill test. The amount of work necessary to produce ischemic ST depression was not consistently increased. The most striking physiologic effect of propranolol was a decrease in heart rate both at rest and on exercise. Blood pressure on exercise also fell.

Frieden,[13] in a review of 200 cases of angina pectoris treated with propranolol, reported general improvement in over half of the subjects when adequate dosages were used. Less benefit was noted when the dose was less than 120 mg/day.

Hebb[14] conducted a double-blind study of propranolol in the prophylactic treatment of angina pectoris. Patients received either a placebo or propranolol for four weeks. The dose of propranolol was 40 mg/day for the first week, 80 mg/day for the second week, and 160 mg/day for the third and fourth weeks. No significant reduction in the attack rate occurred at the 40-mg/day dose, but with 80 mg/day the reduction was significant ($p < .05$), and at 160 mg/day it was very significant ($p < .001$).

Combination Therapy

The rationale for combining propranolol with the nitrates rests on the belief that nitrates increase oxygen supply to ischemic myocardium, while propranolol, by decreasing heart rate and ventricular systolic force, appears to reduce myocardial oxygen requirements to a level more readily satisfied by restricted coronary flow.

Russek[15] studied 12 patients with exertional angina of at least two years' duration with placebo, isosorbide dinitrate (Isordil®), propranolol and the combination of Isordil and propranolol. In the standard exercise test, Isordil prevented the onset of pain in four of 12 patients and diminished its severity in seven. Propranolol (40 mg) prevented its onset in three and diminished its severity in nine. Combined therapy prevented all 12 patients from experiencing any discomfort as a result of exercise. Prior to exercise the heart rate after propranolol was 20% below that of placebo, but with Isordil 12% faster. The reduction in maximal heart rate with exercise averaged 25 beats per minute with propranolol alone or in combination with Isordil. In all 12 patients the greatest ST-T depression followed administration of placebo. The average increase in exercise tolerance with propranolol or Isordil alone was 24%, whereas with combination therapy it averaged 76%. All patients were followed for two months with striking relief of symptoms. A second paper by Russek[16] added an additional 16 patients who were followed for six months without evidence of tolerance or escape from the medication.

Side effects from propranolol are uncommon. Death was associated with propranolol administration in 26 of 5000 cases.[17] In only three of the 26 deaths was propranolol suspected as a contributing factor. Since the intravenous form of propranolol became available in our hospital we have experienced three deaths after 5 mg was given for arrhythmia. Two of the patients were in chronic heart failure and shortly after the intravenous administration became hypotensive and refractory to the usual vasopressors even in very large doses (metaraminal (Aramine®)) 200 mg in 500 cc D5W and levarterenol bitartrate (Levophed®) 12 mg in 500 cc D5W. This is not surprising since Aramine is a false transmitter, acting to release noradrenalin at the receptor site now blocked by propranolol. The third patient had a significant element of bronchospasm prior to the administration of the drug. Following the intravenous administration he developed acute bronchospasm which did not respond to conventional therapy.

In those patients in whom heroic measures may be justified, we currently recommend intravenous propranolol 1-2 mg given slowly for control of cardiac arrhythmia.

Early reports of BUN and SGOT elevation have not been confirmed and cases of bone marrow depression have been unusual. Hypotension has been uncommon except in those patients with congestive heart failure. Other investigators have reported protracted hypoglycemia in patients receiving a combination of propranolol and sulfonoureas.

Propranolol is contraindicated in heart block, congestive heart failure, asthma, chronic obstructive lung disease and in patients receiving monoamine oxidase inhibitors.

Summary

Six patients have been described who have responded to propranolol for control of angina pectoris and have thus escaped a surgical procedure with significant morbidity and mortality.

Three other patients have been presented who died shortly after the administration of IV propranolol (5 mg) for control of a cardiac arrhythmia. It is suggested that alternate methods should be utilized for control of arrhythmia in patients with congestive heart failure or hypotension.

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On Posture

It is well when the patient is found by his physician reclining upon either his right or his left side, having his hands, neck, and legs slightly bent, and the whole body lying in a relaxed state, for thus the most of persons in health recline, and these are the best of postures which most resemble those of healthy persons. But to lie upon one's back, with the hands, neck, and the legs extended, is far less favorable. And if the patient incline forward, and sink down to the foot of the bed, it is a still more dangerous symptom; but if he be found with his feet naked and not sufficiently warm, and the hands, neck, and legs tossed about in a disorderly manner and naked, it is bad, for it indicates aberration of intellect. It is a deadly symptom, also, when the patient sleeps constantly with his mouth open, having his legs strongly bent and plaited together, while he lies upon his back; and to lie upon one's belly, when not habitual to the patient to sleep thus while in good health, indicates delirium, or pain in the abdominal regions.

And for the patient to wish to sit erect at the acme of a disease is a bad symptom in all acute diseases, but particularly so in pneumonia. To grind the teeth in fevers, when such has not been the custom of the patient from childhood, indicates madness and death, both which dangers are to be announced beforehand as likely to happen; and if a person in delirium do this it is a very deadly symptom.*

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*Hippocrates: The Book of Prognostics

Nobel Prize Winners in Medicine and Physiology

1927

Julius Wagner-Jauregg

For his discovery of the therapeutic value of
malaria inoculation in the treatment of dementia paralytica

"Progressive paralysis has always been considered an incurable disease, leading in the course of a few years to dementia and death.

"Nevertheless there was on record a series of cases of progressive paralysis which had been cured; cases in which all the symptoms had disappeared so completely as to permit those affected to be independently active for years, in life and employment.

"The observation was now forthcoming that in the rare cases of healing and in the frequent remissions of progressive paralysis, a febrile infectious malady or a protracted suppuration often preceded the improvement in the state of the disease.

"Therein lay a hint. These cures following febrile infectious diseases, of which I myself had witnessed striking cases, induced me as early as the year 1887 to propose that this natural experiment be imitated by deliberately producing infectious diseases, and at that time I named malaria and erysipelas as suitable diseases. As a particular advantage of malaria, I stressed the fact that it is possible to interrupt the disease at will with quinine, and did not yet suspect at that time to what extent the expectation would be fulfilled through inoculation with malaria.

"Instead, starting in 1890, I attempted to imitate the action of a febrile infectious disease by the use of tuberculin, just introduced by Koch, at first not only in progressive paralysis but also in other mental derangements, and as a matter of fact with favorable results in not a few cases.

"After it had been established that the paralytics treated with tuberculin showed more, and more lasting, remissions than an equal number of untreated paralytics, this treatment was carried out systematically . . . and at the same time an energetic iodine-mercury cure, later combined with injections of salvarsan, was instituted.

"The remissions which were obtained by the mercury-tuberculin treatment did not differ qualitatively from those to be obtained by inoculation with malaria. . . . But the number of relapses was large; the lasting remissions were in the minority.

"Consequently, in 1917, I set about the execution of the proposal I had made in the year 1887, and inoculated nine cases of progressive paralysis with tertian malaria.

"The result was gratifying beyond expectation: six of these nine cases obtained extensive remissions, and in three of these cases the remission proved lasting, so that this year (1927) I was able to present these cases as having carried on their occupations without interruption for ten years."*

Wagner-Jauregg appears to have contemplated the use of malaria in treating paretic dementia for many years, and when, in 1917, a patient with tertian malaria appeared in one of his wards he considered this as a sign of fate and proceeded to carry out his plan.†

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*Nobel-Vortrag von Julius Wagner-Jauregg.
†Theodore Sourkes: Nobel Prize Winners in Medicine and Physiology, 1966.

Vaginal Hormonal Cytology

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THE VAGINAL EPITHELIUM is characterized by great sensitivity to the constant interplay of the hormones produced in health or disease. An analysis of the cellular patterns of exfoliated vaginal cells offers the clinician an opportunity for greater understanding of a woman's endocrine status.

Historical

Pouchet, as early as 1847 in his book *Ovulation and Other Related Phenomena,* gave one of the first descriptions of vaginal smears. Although he had no staining technique to aid him, he was able to recognize a rhythmic change in the vaginal smears.[1] By 1917, Stockard and Papanicolaou[2] described the periodic changes of the constituents of the vaginal smear in the guinea pig, stimulating an interest in study of these changes in the lower animals.

Dierks,[3] studying specimens of vaginal epithelium taken for biopsy, offered the first definite proof of the susceptibility of the epithelium to ovarian secretions. He demonstrated the proliferation of vaginal epithelium in oophorectomized women after the injection of "follicular hormone."

In 1933 Papanicolaou[1] described the staining technique which now bears his name. He presented an analysis of 1,022 vaginal smears obtained from 12 normal menstruating females and 16 patients who had been operated upon for different reasons. In his analysis, a correlation was noted between cytology changes and time of cycle or ovarian status at the time of operation.[1]

Collection of the Smear

A well-prepared smear should be spread neither too thick nor too thin, fixed rapidly and stained correctly,[4] since the diagnostic possibilities depend on the quality of the smear.

Several sites in the vagina have been proposed as ideal for obtaining smears for hormonal evaluation.[5,6] Even study of the urine sediment has been suggested as a method for evaluation of the hormonal status of the patient.

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The upper third part of the lateral vaginal wall provides the freshest and most satisfactory material for the procedure.[5-8] The sample should be obtained with the help of a dry speculum to avoid contamination of the specimen by vulvar and cervical secretions.[9] A cervical smear for detection of malignant cells may be taken at the same time, when indicated. The cervical smear should be taken after the vaginal sample has been obtained, so as not to contaminate the hormonal smear with cervical elements. A wooden spatula is used to scrape the vagina lightly; the material thus obtained is spread on a glass slide which is deposited in a fixative solution containing equal parts of alcohol and ether, or 95% alcohol.[10]

Staining of the Smear

Since Papanicolaou's classical description of his staining technique, several others have been developed,[11,12] most of them with the objective of improving the rapidity of the technique and the color reactions which serve to distinguish the basophilic and eosinophilic cells.

A supravital* technique has been recommended by Rakoff[11] as a rapid stain for office use:

a. Obtain a sample from the vaginal wall with a cotton-tip applicator, preferably dipped previously in a container of 2 cc of isotonic solution of sodium chloride.

b. Drop the applicator into a container of sodium chloride.

c. Add 3 drops of a staining fluid composed of 83 cc of light green 5% aqueous solution and 17 cc of eosin (1% aqueous solution).

d. Agitate the cotton swab in the solution, transfer a drop of the solution to a glass slide and examine under the microscope.

Disadvantages of this supravital technique are the instability of the solution, requiring frequent reconstitution, and the impossibility of keeping the slides for permanent record.

Elements Found in a Normal Smear

Under physiologic conditions smears may contain three different types of cells which correspond to cells in the three layers of the vaginal mucosa.

Parabasal Cells

These are the least mature cells found in a smear. They are small, round and basophilic, with a vesicular nucleus which occupies more than a third of the diameter of a cell. They resemble cervical cells, from which they must be distinguished. Parabasal cells are found in association with absence of estrogens, postmenopausal states, hypopituitarism, postpartum states, and in severe vaginal infection or trauma.

Intermediate Cells

These cells originate from the intermediate layer of the vaginal epithelium and are larger than parabasal cells. They are basophilic polygonal cells, with a thin, vacuolized cytoplasm and a vesicular nucleus. The presence of intermediate cells in the smear is determined by the presence of progesterone. Thus they are characteristic of the luteal phase of the cycle and of the smear obtained during pregnancy. They can be found under the influence of androgenic hormones.

Superficial Cells

These are the largest and most mature cells seen in a vaginal smear. They are polyhedral and flat, with a pyknotic nucleus, and stain red with a polychromatic stain. The appearance of superficial cells is titrated by the unopposed action of estrogens.

Other elements which can be found in vaginal smears include cervical and endometrial cells, *Candida albicans and Trichomonas vaginalis.*

Interpretation of Cytologic Results

Several indices based on this procedure may be of assistance in the determination of the hormonal status. Of these, three will be described.

Karyopyknotic Index

The karyopyknotic index refers to determination of the percentage of cells which have a pyknotic nucleus: that is, a nucleus which measures less than 6 micra, without an identifiable chromatin pattern. This is a reliable index because nonhormonal factors have little effect upon it.

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*See Test Your Word Score Page 759.

Eosinophilic Index

The eosinophilic index is the percentage of eosinophilic cells counted from a least 200 superficial cells. Since pseudoeosinophilia may be produced by vaginal infections, drying of the slide, or prolapse of the vagina, this index is useful only when it parallels the karyopyknotic index.

Maturation Index

This index involves the estimation of the percentage of each of the three types of exfoliated cells found. It is reported by three numbers which correspond from left to right to the parabasal, intermediate and superficial cells.

Normal Menstrual Cycle

The presence of erythrocytes, leukocytes, intermediate and superficial cells exemplify the menstrual phase of a normal menstrual cycle. The normal karyopyknotic index is then between 20 and 50%, the eosinophilic index 5 to 20%, and the maturation index 0/70/30.

Preovulatory Phase

Isolated superficial cells with a clean background free of Döderlein bacilli are typical of a high estrogenic effect. It comes about gradually, the intermediate cells being replaced by superficial ones having a higher number of pyknotic nuclei. The indices representative of this preovulatory phase are: eosinophilic index 70%, karyopyknotic index 70 to 85%, maturation index 0/20/80.

Detection of Ovulation

Ovulation may be detected as early as six hours after it has occurred by noting the decrease of the eosinophilic index and the karyopyknotic index. This means obtaining two or three smears daily from the patient, especially in the preovulatory interval.

Progesterone Effect

The changes caused by progesterone, representing the secretory phase of the cycle, become definite 48 hours after ovulation. The typical smear obtained at that time exhibits a predominance of intermediate cells which tend to group themselves in clusters. There is a reappearance of leukocytes and Döderlein bacilli as well as large amounts of cellular detritus which give to the slide a "dirty background." Eosinophilic cells with pyknotic nuclei become scarce and isolated. The indices are eosinophilic index 15%, karyopyknotic index 30% and maturation index 0/70/30.

It is of practical interest to report the findings of the Gillespies'[13] study of 300 vaginal smears. A correlation was established between the maturation index estimated by a cytotechnician and that estimated by the attending obstetrician after a superficial scanning of the smear. The difference between the two estimates was in the range of 10%.

Clinical Syndromes

Climacteric

The term "climacteric" corresponds to the transition period of ovarian decline during which the menstrual periods cease and the characteristic vasomotor changes, nervousness and so on, appear.[14]

De Neef[4] described three types of smears that can be obtained in women near the menopause. Others[15,16] have written that there is no smear pathognomonic of this state. Smears range from those disclosing advanced atrophy, in which only parabasal cells are found (maturation index 80/20/0), to those exhibiting hyperestrogenic changes (maturation index 0/20/80). Peters[17] obtained smears reflecting estrogenic changes from 53% of women younger than 55 years, and similar smears from 37% of patients older than 55 years. However, the possible presence of an estrogen-producing ovarian tumor, such as the granulosa-cell tumor, should always be kept in mind when a smear suggestive of estrogenic effect is seen. The ingestion of digitalis preparations is another mechanism by which a smear connoting estrogen production may be obtained in the postmenopausal woman.

Estrogen Therapy

Much has been written in the lay press about the use of hormonal colpocytology* to regulate the administration of exogenous estrogens. A decision to use sedation as the basic treatment of a patient complaining of hot flashes may follow the finding of estrogenic effects in her smear. On the other hand, the association of climacteric complaints and a smear which reflects vaginal atrophy is of value to the clinician as an indication for therapy with estrogen. Gaudefroy,[16] studying the effects of varying doses of different estrogens, concluded that therapeutic doses produce proliferation with karyopyknosis of the superficial cells. This raises the karyopyknotic index to 90% as early as 48 hours after the first dose. A karyopyknotic index higher than 70% should not be sought, because vaginal bleeding frequently occurs when the index exceeds that figure.[4]

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*See Test Your Word Score Page 759.

Menstrual Disorders

Smears typical of atrophy in patients who have primary amenorrhea point to a pituitary lesion, Turner's syndrome or other causes of which the lack of estrogen production is a major sign. Detection of a cyclical estrogen-progesterone effect in the smears from these patients indicates the integrity of the pituitary-ovarian axis. Such a finding would mean that the diagnosis of unresponsiveness of the endometrium or congenital absence of the uterus might be entertained.

Pregnancy

Although advocates of hormonal colpocytology say that the procedure permits the diagnosis of pregnancy shortly after conception has occurred, most authors agree that a typical pregnancy smear cannot be obtained until after the first trimester of gestation.[18,19] To quote Von Haam's[9] opinion of the procedure thus employed: "The diagnosis of pregnancy by the vaginal smear method is feasible but impractical since quicker and more reliable methods are available."

Threatened Abortion

During pregnancy the smears will reveal the increase of progesterone by showing increasing numbers of glycogen-rich intermediate cells which have a characteristic navicular form, clear cytoplasm, heavy outline and a round, vesicular nucleus. The number of these cells increases greatly after the fourth month of pregnancy, while the number of superficial cells decreases substantially. The representative indices are not higher than 15% (eosinophilic index) or 20% (karyopyknotic index). The maturation index is 0/80/20. A change from a normal pregnancy smear to a smear suggestive of estrogenic influence has been considered a prelude of abortion.[20]

Pundel,[21] studying 3,800 pregnant women, found 407 from whom vaginal smears reflecting abnormalities were obtained; 117 of these women had no clinical evidence of threatened abortion. All 117 patients were offered hormonal therapy on the basis of studies of the smears alone; 28 refused it. The outcome of the pregnancies was revealing: of the 28 untreated patients 14 aborted (50%); of the 89 treated patients only 21 aborted (22%). On the other hand, Pundel reported that normal term pregnancies ensued for 99.41% of 3,393 pregnant women in whom cytologic studies yielded normal results.

Placental Nonfunction

Knowledge that estrogens administered during a pregnancy in which the fetus is viable do not produce maturation of the vaginal mucosa, thereby failing to increase the eosinophilic index and karyopyknotic index, has led to the development of a sensitive test for determination of the death in utero of a fetus. An increase in the eosinophilic and karyopyknotic indices is a sign of placental nonfunction. This same principle can be employed in the differential diagnosis between imminent menopause and pregnancy in a patient with amenorrhea.

Ruptured Membrane

The finding of anucleated squamous cells in a smear from a pregnant patient in whom uterine prolapse or leukoplakia of the cervix has been ruled out is positive evidence of rupture of the membranes. Use of the hormonal colpocytologic procedure to determine term pregnancies,[22] to predict labor[23] and to predict the sex of the infant is of equivocal value and is simply mentioned here.

Hormonal Cytologic Studies in Children

Under the influence of the maternal hormones, the vaginal epithelium of the newborn has a thick and well-developed intermediate layer which is lost a few days after birth. It remains as a thin layer of basal cells until shortly before the onset of puberty.

The local or systemic administration of estrogens, frequently employed in the treatment of vaginitis in children, is often the reason for vaginal smears in the prepuberal female to show features reflecting stimulation by estrogen. Other causes for this activity reflected in smears include sexual precocity, feminizing tumors of the ovary and conditions of stress.

Summary

The known sensitivity of the vaginal epithelium to the effects of hormonal activity in the presence of both health and disease constitutes a source of some diagnostic value to the clinician when it is studied and appraised by means of analysis of the cellular patterns of exfoliated vaginal cells. The procedure is uncomplicated, inexpensive and reliable. Those conditions in which the procedure will give significant results, as well as those in which it is of only theoretical or doubtful value, have been reviewed briefly here.

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On Sleep

With regard to sleep—as is usual with us in health, the patient should wake during the day and sleep during the night. If this rule be anywise altered it is so far worse: but there will be little harm provided he sleep in the morning for the third part of the day; such sleep as takes place after this time is more unfavourable: but the worst of all is to get no sleep either night or day; for it follows from this symptom that the insomnolency is connected with sorrow and pains, or that he is about to become delirious.*

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*From Hippocrates' Book of Prognostics.

Don't relive bad moments or review them for others.—Marianne Moore

A Patriarch's Ordeal

Poor Job! None the less to be commiserated with whether his afflictions were malevolent visitations or psychosomatic manifestations of utter despair!

A catalogue of his woes is horrendous—not so much in severity as in obduracy. The milieu for his trial was set by two personal calamities: first, his oxen, asses and camels were caused to be stolen (the word "caused" is here used advisedly); and second, his servants and sons were killed off. At this nadir of destitution and bereavement Job's harrowing physical and psychical ordeal began.

First came boils! One boil would be bad enough, but Job was literally covered "from the sole of his foot unto his crown." With no doctor at hand, he dealt with the boils himself by scraping them with a potsherd (a shard of broken pot)—a procedure that hardly sounds therapeutic and must have aggravated rather than alleviated the acute discomfort.

Following the boils came hallucinations: "Then a spirit passed before my face; the hair of my flesh stood up: It stood still, but I could not discern the form thereof: an image was before mine eyes."

Then insomnia and nightmares ensued: "I am full of tossings to and fro unto the dawning of the day. Then thou scarest me with dreams."

These were succeeded by more skin disorders: "My flesh is clothed with worms; my skin is broken and become loathsome."

Then, as if he had not undergone sufficient suffering and humiliation, his wounds were exacerbated and he had trouble breathing: "For he breaketh me with a tempest, and multiplieth my wounds without cause. He will not suffer me to take my breath."

Next, to add insult to injury, he developed wrinkles: "And thou hast filled me with wrinkles, which is a witness against me: and my leanness rising up in me beareth witness to my face."

A sequence of shocking assaults next descended upon him: "He hath broken me asunder: he hath also taken me by the neck, and shaken me to pieces, and set me up for his mark. He cleaveth my reins asunder, and doth not spare; he poureth out my gall upon the ground. He breaketh me with breach upon breach, he runneth upon me like a giant."

The sense of frustration, alienation and repudiation that resulted from his relentless persecution was abysmal! "But now they that are younger than I have me in derision. They abhor me, they flee far from me, and spare not to spit in my face."

But what appeared to be the proverbial "last straw" still did not end Job's appalling endurance test. He had yet to undergo one final shattering assault: "My bones are pierced in me in the night season: and my sinews take no rest. By the great force of my disease is my garment changed: it bindeth me about as the collar of my coat. He hath cast me into the mire, and I am become like dust and ashes. My bowels boiled and rested not. My skin is black upon me, and my bones are burned with heat."

We wholly conquer only what we assimilate.—Gide

Toxoplasmosis and Pneumocystis Carinii Pneumonitis

in a Patient with Chronic Lymphatic Leukemia

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Opportunistic protozoal and fungal infections occur in patients with lymphoreticular or hematopoietic malignancies treated with corticosteroids, radiation, alkylating agents, and antimetabolites. The prolongation of life provided by these therapies has been shadowed by uncommon complications associated with changes in the immune mechanism. New clinical entities have evolved under these circumstances. This is demonstrated by a patient with chronic lymphatic leukemia of nine years duration who died because of two unusual infections: toxoplasmosis and pneumocystis carinii pneumonitis. Early recognition of such infections is of utmost clinical importance, because they may be potentially curable.

Case Report

A 50-year-old man had a seminoma of the left testis removed in 1954, followed by radiation therapy to the pelvis and abdomen. In 1959 the diagnosis of chronic lymphatic leukemia was established by peripheral blood examination and biopsy of a cervical node. Radiation therapy was given to the cervical, axillary, and inguinal nodes.

He was well until January 1962, when anemia developed. Blood transfusions were administered, and in March 1962, an enlarged spleen was treated with radiation therapy. Oral iron and corticosteroids were given.

When first seen at the University of Minnesota Hospitals in April 1962, there was generalized lymphadenopathy and hepatosplenomegaly. The hemoglobin was 6.4 g/100 ml, leucocytes 10,950 per mm^3 with 71 percent mature lymphocytes, and the platelets were 62,000 per mm^3. Mild hemolysis was noted. A bone marrow biopsy revealed erythroid hypoplasia, a decreased number of granulocytes and megakaryocytes, and lymphocytosis.

Treatment

Therapy with 40 mg of prednisone was begun and in May 1962, testosterone enanthate, 600 mg twice a week intramuscularly, was added. The hemoglobin increased over the next five months to 18 g/100 ml. Erythrocytosis as a response to androgen therapy was previously reported.[1]

The disease remained controlled with prednisone and

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testosterone enanthate until April 1967, when generalized lymph node enlargement and hepatosplenomegaly recurred. The hemoglobin was 14.3 g/100 ml, leukocytes 56,300 per mm^3 with 96 percent lymphocytes, and platelets 196,000 per mm^3. Serum electrophoresis showed 0.2 g percent of gamma globulin. Treatment included prednisone and uracil mustard; later cyclophosphamide was added. In September 1967 progression of the disease was partially controlled with radiation therapy to the mediastinal lymph nodes and subsequently vinblastine sulfate.

Progress

On December 5, 1967, he was admitted because of progressive weakness and fever. There were multiple superficial ulcerations of the oral mucosa and lips and necrotic ulcerated areas of the skin with petechiae and ecchymoses on the extremities. Multiple soft, nontender 0.5 to 1-cm cutaneous nodules were present throughout the body. There was generalized lymphadenopathy, right pleural effusion, hepatosplenomegaly, and 4 + pitting edema in the lower extremities.

The hemoglobin was 9.0 g/100 ml, leukocytes 5,650 per mm^3 with 50 percent lymphocytes, reticulocytes 3.5 percent, and platelets 49,000 per mm^3. Urinalysis showed granular and hyaline casts. The BUN was 41 mg/100 ml, creatinine 1.7 mg/100 ml, total bilirubin 0.8 mg/ml, serum alkaline phosphatase 10 KAU/100 ml, and serum lactic dehydrogenase 544 IU/liter (126 IU/liter heat stable). The prothrombin time was 13.7 seconds, the serum fibrinogen was 0.2 gm percent. Roentgenograms of the chest demonstrated anterior mediastinal masses and right pleural effusion obscuring the pulmonary parenchyma. In the left lung there was a perihilar infiltrate suggestive of pulmonary edema or pneumonitis. This infiltrate showed significant resolution four days later.

Skin tests for tuberculosis, histoplasmosis, blastomycosis, and coccidiomycosis were negative. A culture of the sputum showed growth of many coagulase-positive staphylococci, many Leisseriae species, many alpha streptococci and a few gamma streptococci. Sputum cultures for fungi grew Candida albicans. There was no growth on the blood, urine, and pleural fluid cultures. The pleural fluid was hemorrhagic. Culture of a skin ulcer grew many coagulase-positive staphylococci.

On the third hospital day anterior chest pain occurred; subsequently electrocardiographic and enzyme changes were consistent with the diagnosis of a recent small anterior myocardial infarction.

The hospital course was characterized by fever, cough, respiratory distress, increasing weakness and confusion. Antibiotics, corticosteroids, diuretics, and blood transfusions were administered. The patient expired 18 days after admission.

Pathologic Findings

Gross

At autopsy there were subcutaneous nodules, lymphadenopathy, hepatosplenomegaly, and bilateral hemorrhagic pleural effusion. The heart weighed 310 gm and the myocardium showed a slightly mottled yellowish discoloration in the left ventricle; the coronary arteries had marked arteriosclerotic narrowing; the left circumflex artery was narrowed almost to occlusion just beyond its origin. The appearance of the lungs was suggestive of pulmonary edema with foci of pneumonitis. The brain disclosed prominent blood vessels, particularly in the white matter of the cerebral hemispheres, consistent with congestion. In the white matter of the temporal and occipital lobes there were faintly grey, punctate areas.

Microscopic

On microscopic examination the lymph nodes, liver, spleen, and bone marrow were involved by a lymphomatous process. The lungs showed increased numbers of macrophages within the alveoli in the absence of polymorphonuclear leukocytes, lymphocytes or plasma cells. Some alveoli contained, in addition, a fibrillar, eosinophilic material. Small clusters of eosinophilic, slightly grayish bodies, each about six microns in size, were found, sometimes in association with this material, but more often lying along alveolar walls. A Grocott-Gomori's methenamine silver nitrate stain confirmed that these bodies were Pneumocystis carinii organisms (Figure 1). The alveolar septa were variably widened due to congestion or edema, but they did not contain an inflammatory cell infiltrate.

In the myocardium there were foci of chronic inflammatory cells between muscle fibers consistent with a mild myocarditis. Occasional widened myocardial fibers contained clusters of small organisms, each less than two microns in size. These "psuedocysts" contained a hundred or more microorganisms, and their appearance was that of myocardial toxoplasmosis (Figure 2). No free organisms could be found.

The brain revealed widespread reactive microglial* foci in all parts, often surrounding blood vessels and occasionally associated with central areas of necrosis. Pseudocysts of Toxoplasma gondii were found in the absence of any reaction in all sections of brain studied (Figure 3) and occasionally with the microglial foci. Free toxoplasma organisms were found in one small area. The areas of necrosis and microglial reaction were considered unrelated to the presence of toxoplasma organisms. The neuropathological diagnosis was meningoencephalitis probably of viral etiology, and toxoplasma organisms in the brain.

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*See Test Your Word Score Page 759.

Discussion

A patient with chronic lymphatic leukemia during the nine-year duration of the illness received radiation therapy, corticosteroids, alkylating agents, and vinca alkaloids. During one phase of the disease, erythroid hypoplasia improved dramatically with massive doses of an androgen. While the disease was in exacerbation, he developed fever, progressive confusion, cough, respiratory distress, and then died. At post-mortem examination Toxoplasma gondii was discovered in the brain and myocardium, and Pneumocystis carinii was found in the lungs.

Patients with lymphoma, Hodgkin's disease, or leukemia treated with corticosteroids, chemotherapeutic agents, and radiation develop in the course of their disease new symptoms and signs from the brain, lungs, myocardium, liver, kidneys, and bladder. Three diagnostic possibilities are usually considered: progression of the disease, drug toxicity, and superimposed infection.

Infections

Opportunistic infections with bacteria, viruses, fungi, and protozoa of limited pathogenicity for healthy individuals are frequently the cause of death in these debilitated patients. Some of these infections are treatable and potentially curable.

Infection in the adult with the protozoan, Toxoplasma gondii, can involve several organs and give a great variety of clinical manifestations. This infection can be glandular, involving only the lymph nodes, miliary with widespread dissemination, or localized, affecting one or two organs.[2] There have been an increasing number of reports of toxoplasmosis complicating malignancies especially of the lymphoreticular and hematopoietic tissues.[3-5]

Malignancy

Toxoplasmosis associated with malignancy and involving the brain and myocardium has been observed.[5] The involvement of the brain

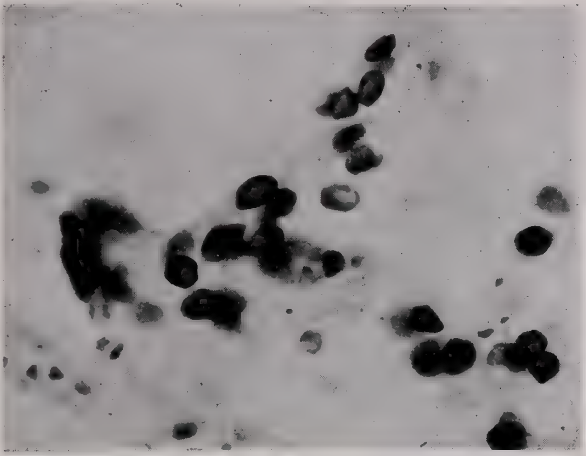

Fig. 1—A cluster of pneumocystis organisms within an alveolus. The dark-staining saccular cystic forms contain a pair of "parentheses-like" bodies. Connections at the ends of the structures form "rings." Crocott-Gomori methenamine silver nitrate stain, magnification 800 x.

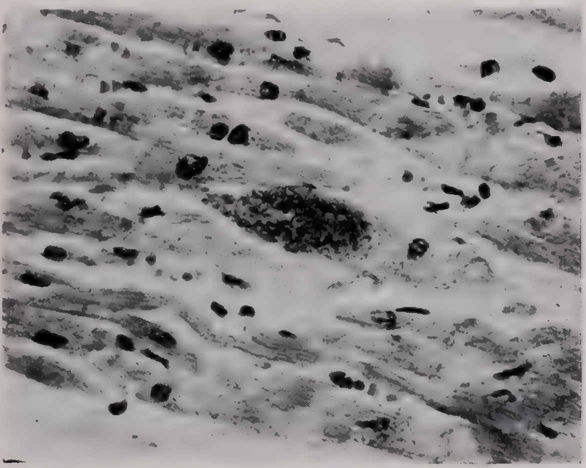

Fig. 2—A pseudocyst of toxoplasma organisms within a myocardial fiber. H and E stain, 400 x magnification.

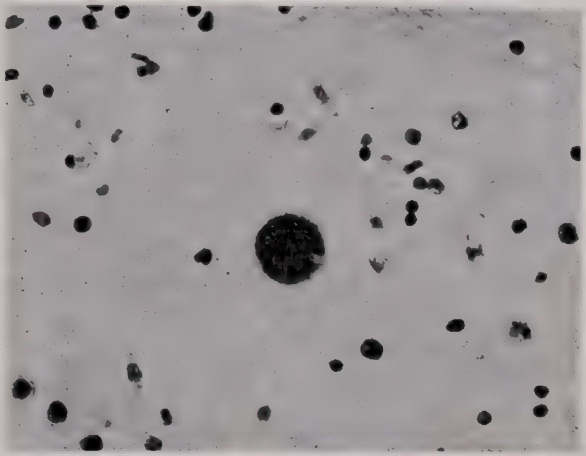

Fig. 3—A pseudocyst of toxoplasma organisms in brain tissue. Inflammatory and glial reaction is absent. H and E stain, 320 x magnification.

may manifest itself either as a diffuse or focal encephalitis or as a space-occupying lesion.[3] The electroencephalogram may show diffuse or focal abnormalities, and the cerebrospinal fluid frequently shows elevated pressure and protein values, and pleocytosis. The myocardial involvement may remain subclinical or manifest itself as myocarditis with cardiac enlargement, tachycardia, arrhythmias, gallop rhythm, heart failure, and electrocardiographic changes.

Our patient had progressive mental confusion but no focal neurologic manifestations. He had mild congestive heart failure, and on the fourth hospital day electrocardiographic changes were consistent with a myocardial infarction. Although the myocardial toxoplasmosis may have contributed to the initial congestive heart failure, the old occlusion of the circumflex coronary artery and the anemia may also have been contributory factors.

Mixed infection with Toxoplasma gondii and cytomegalovirus have been observed with unexpected frequency in patients with advanced malignant disease.[5] This mixed infection with a protozoan and a deoxyribonucleic acid virus has been studied recently in vitro in human fibroblasts.[6] An unusual patient with toxoplasmosis of the lung and stomach, herpetic esophagitis, cytomegalic inclusion disease of the lung, and sarcocystis infection of the heart has been reported.[7]

When toxoplasmosis is suspected, the diagnosis can be made by a rising titer of anti-toxoplasma antibodies detected with the Sabin-Feldman dye test, a hemagglutination and a complement fixation test, and more recently as 19S and 7S anti-toxoplasma antibodies with the 19S demonstrable in the acute phase sera.[8] Occasionally free and encysted organisms can be seen in biopsy sections, and they might be isolated following inoculation of infected tissue or body fluids into the peritoneal cavities or the brain of mice.

*Taxonomy**

There is no general agreement for the taxonomic classification of Pneumocystis carinii.[9] The morphology of this organism and the susceptibility to pentamidine therapy have been the main factors in accepting this parasite as a protozoan. However, strong evidence has been advanced for a fungal nature.[10]

Pneumocystis carinii infection in humans demonstrates a limited range of tissue specificity involving almost exclusively the lungs. It manifests itself clinically and pathologically as an interstitial pneumonitis. The disease is common in debilitated premature infants, but it has been considered a rare nosologic entity in adults.[11,12]

Most of the reported cases in adults have been observed in patients with lymphoreticular and hematopoietic malignancies after prolonged administration of antibiotics, corticosteroids, cytotoxic chemotherapy, or radiation therapy.[12,13] Certain cases have been associated with secondary immunological deficiency states resulting from immunosuppressive therapy following kidney transplantation.[14] Our patient had a low serum gamma globulin level.

Subclinical

The Pneumocystis carinii pneumonitis in the adult may remain subclinical or may have an insidious onset with increasing cough, fever, tachypnea, dyspnea, and cyanosis. The findings on physical examination are limited to the chest, with scattered rales occasionally present. The pathophysiology of the disease is the result of an alveolar capillary block secondary to inflamed and thickened alveolar septa.[9] Pleurisy and pleural effusions have not been reported with this pneumonia in adults. In our patient the pleural effusion was associated with the malignant process.

Most of the reported cases of pneumocystis pneumonitis in adults were diagnosed incidentally at autopsy. Recently, with an increasing awareness of this clinical entity, the disease is suspected antemortem. X-ray findings of diffuse bilateral interstitial pneumonitis and the pulmonary function findings of alveolar capillary block are suggestive of the process. The diagnosis can be established only by the identification of the pneumocystis cysts in the sputum, in hypopharyngeal aspirates, in percutaneous lung aspiration biopsy or in open-chest lung biopsy. Laboratory tests have been of no value, and an introduced complement fixation test needs additional evaluation. Since this infection appears potentially curable, early recognition is important.

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*See Test Your Word Score Page 759.

Concomitant infections with Pneumocystis carinii and cytomegalovirus have been reported with surprising incidence.[13,14] Mixed infections with Aspergillus, Nocardia, Candida albicans, and Histoplasma capsulatum have been observed.[13,14] Combined toxoplasmosis and Pneumocystis carinii pneumonitis in the same patient has not been reported.

Summary

Chronic lymphatic leukemia in an adult male was controlled for nine years by treatment with radiation, corticosteroids, alkylating agents, vinca alkaloids, and androgens. During a period of exacerbation of the disease the patient died following an acute illness with fever, cough, dyspnea, progressive weakness, and confusion. Post-mortem examination demonstrated toxoplasmosis of the brain and myocardium and pneumocystis carinii pneumonitis.

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Advice from a Medieval Physician

And of those things which are incumbent on the student of this Art (Medicine) are that he should constantly attend the hospitals and sick-houses; pay unremitting attention to the conditions and circumstances of their inmates, in company with the most acute professors of Medicine; and enquire frequently as to the state of the patients and the symptoms apparent in them, bearing in mind what he has read about these variations, and what they indicate of good or evil. If he does this, he will reach a high degree in this Art. Therefore it behooves him who desires to be an accomplished physician to follow closely these injunctions, to form his character in accordance with what we have mentioned therein, and not to neglect them. If he does this, his treatment of the sick will be successful; people will have confidence in him and be favourably disposed towards him, and he will win their affection and respect and a good reputation; nor withal will he lack profit and advantage from them. And God Most High knoweth best.*

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*Ali ibnu 'l-Abbas, Persian physician.

Illusions

Don't part with your illusions. When they are gone you may still exist, but you have ceased to live.—Mark Twain

Famous Men and Their Bad Health

Thomas de Quincey

De Profundis

"Ecce, this child has been in hell!" So spoke Coleridge of his friend Thomas De Quincey, the English opium addict. No other seven words could have said more!

For thirty years, beginning as a student, Thomas De Quincey (1785-1859) took opium for respite from the throes of excruciating facial neuralgia accompanied by agonizing toothache. Out of his long ordeal of addiction came his Confessions, written to show the medical value of opium as a pain reliever and to reveal its mastery over the mind dream-wise. During the depths of his thralldom his biographer, Horace Eaton, says that De Quincey kept a decanter of laudanum constantly at his elbow, his daily dosage at one time ultimating to 8,000 drops, the equivalent of 300 grains of opium.

The Confessions of an English Opium Eater is an open sesame to that fantastic other-dimensional dream world whose door only a powerful drug can open—and also close after admittance. So cogent is De Quincey's literary magic that when we read the Confessions we lose our personal identity and merge with the author in his compulsive descent to Avernus. Not all the dreams are hideous phantasmagorias; some are glorious extravaganzas; yet all alike are permeated with a sense of Final-Judgment doom.

"I seemed every night to descend, not metaphorically, but literally to descend into chasms and sunless abysses, from which it seemed hopeless that I should ever reascend. Not did I, even by waking, feel that I had reascended."

After thirty years of seduction by and dependence on opium De Quincey finally conquered the habit. Of the interval between bondage and freedom he said:

"During the whole period of diminishing the opium I had the torments of a man passing out of one mode of existence into another. The issue was not death, but a sort of physical regeneration."

Revelations are rare! For the unique one presented in the Confessions we are forever indebted to Thomas De Quincey.

Levity in Medical Writing

I would never suggest that the physician writer not take his medicine seriously. I do hope, however, he will occasionally laugh at himself, amuse his readers when it helps to get and to hold their attention, warm up his facts before he serves them, and use humor whenever it adds a touch of humanity.

—Richard L. Reece, M.D.

It is Difficult

As Sam said, "You can't no more explain what you don't know, than you can come back from where you ain't been."

Cheese

The main difference between Swiss cheese and Camembert is that the ventilation is a little better.—Anon.

I'll say this for adversity: people seem to be able to stand it, and that's more than I can say for prosperity.—Frank McKinney Hubbard

Treatment of Myocardial Infarction

in a Coronary Care Unit

LORENZO F. TRAJANO, M.D.*
DAVID A. BERMAN, M.D.*
BENJIE GOLDFARB, M.D.*
MARY B. STARK, B.S., R.N.*
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STIMULATED BY REPORTS of reduction in mortality from acute myocardial infarction in patients treated in a coronary care unit we established such a unit at Mt. Sinai Hospital in September, 1966.

The unit proved valuable in treatment of patients with acute myocardial infarction and other problems, such as cardiac arrhythmias, postoperative heart surgery, and artificial pacemakers. Of 280 patients treated during the first year, 146 were suspected to have myocardial infarctions and, of these, 100 had proven myocardial infarctions with electrocardiographic and enzyme abnormalities.

In the 100 patients with acute myocardial infarction treated in the coronary care unit the hospital mortality was 21 per cent. During the same period among 39 patients with acute myocardial infarction not treated in the unit the mortality was 32 percent. During the year prior to the establishment of the unit the mortality of 161 patients with acute myocardial infarction was 34 percent. Most of the improvement in mortality was due to more effective treatment of arrhythmias. Seven of eleven patients who developed ventricular fibrillation were successfully resuscitated; they all recovered without signs of brain damage and were subsequently discharged from the hospital. These results compare favorably with those reported by others as shown in Table 1. The incidence of arrhythmias and other complications is shown in Table 2, with corresponding postmortem findings.

Comment

In hospitals with established coronary care units the mortality of acute myocardial infarction varies but is markedly reduced compared to the pre-coronary care unit era. The successful operation of a coronary care unit depends to a large degree on the nurses. In emergency situations they must be prepared to apply external cardiac massage, mouth-to-mouth respiration, and external counter-shock defibrillation. We have been fortunate in having a devoted and enthusiastic group of nurses who have accepted this responsibility, even though it goes beyond the boundaries of traditional nursing care.[8]

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*From the Department of Medicine, Mount Sinai Hospital, Minneapolis, Minnesota. Presented at the Minnesota Society of Internal Medicine, Duluth, Minnesota, May, 1968.

Lown and his colleagues have shown that ventricular fibrillation (as a primary event) can be almost eliminated by treatment of rhythm disturbances, particularly multiple premature ventricular contraction (especially "R on T" variety), second or third degree heart block, and marked sinus bradycardia.[9] The present treatment of these complications includes intravenous lidocaine, intravenous catheter pacemaker, and atropine or isoproterenol.

The coronary care unit has so far not reduced the dismally high mortality resulting from cardiogenic shock.

Summary

The mortality of acute myocardial infarction at Mount Sinai Hospital in Minneapolis has been reduced by the coronary care unit. Most of the improvement in mortality has been due to more effective treatment of arrhythmias.

TABLE I

Hospitals	No. of Myocardial Infarctions	Period Covered	Days Monitored (Average)	Control Patient Mortality	Monitored Patients' Mortality	Resuscitation	
						At-tempts	Suc-cesses
Toronto, General Hospital, Canada[1]	789	March 13, 1962 to March 12, 1967	5	40%	235(30%)		16(15%)
Bethany Hospital Kansas City, Kansas[2]	411	May 20, 1962 to May 20, 1967	5	34%	85(20%)	46†	31(67%)
Royal Infirmary Edinburgh, Scotland[3]	400	April 18, 1966 to May 10, 1967	3	22%	70(18%)		23(52%)
Royal Melbourne Hospital, Australia[4]	300	1967	3‡	34%	82(27%)	26†	8(31%)
New York Hospital Cornell University Medical Center[5]	250	Jan., 1965 to Dec., 1966	5	30%	32(32%)¶ 37(25%)#	30 36	4(13%) 7(20%)
London Hospital London, England[6]	150	Nov., 1965 to Dec., 1966	3		21(14%)	25	10(40%)
Peter Bent Brigham Hospital, Boston, Mass.[7]	300	1967	5		53(18%)		
Mt. Sinai Hospital Minneapolis, Minn.	100	Sept. 9, 1966 to Dec., 1967	5	34%	21(21%)	16	7(44%)

†Ventricular fibrillation.
‡72 hours after last episode of chest pain or until any severe arrhythmia had been adequately controlled.
¶Initial 100 patients.
#Subsequent 150 patients.

TABLE 2

Complications: 100 Cases	No.	Mortality (21)	Autopsy (10)	
I. Arrhythmias: Except Sinus Tachycardia, 1st Degree A-V Block and PVC's of less than 6 per minute	73	12	8	
A. PVC's of 6 or more per minute	39	5		
B. Atrial Arrhythmias	25	5	(2) (1)	Inferior-lateral infarct No definite occlusion or infarction
C. Vent. Tachycardia: Runs of 3 or more per minute Documented — 8 Observed — 10	18	3	(1) (1)	Subendocardial infarct Inferior-lateral infarct
D. 2nd and 3rd Degree Block	14	3	(1) (1)	Acute hemorrhage, l. circumflex coronary artery Massive infarct, left vent. and septum
E. Ventricular Fibrillation: Exceptions are burst of Vent. Fibrillation as part of Agonal Rhythm	11	4	(1) (1) (1)	Subendocardial infarct No definite occlusion or infarction Ruptured septum
F. Nodal Rhythm	7	0		
G. Sinus Bradycardia: Vent. rate less than 50	6	1		
H. Asystole	3	3	(1) (1)	Inferior-lateral infarct Ruptured ventricle
II. Congestive Failure: Rales, Diastolic Gallop, and Radiological changes	32	6	(2) (1)	Inferior-lateral infarct Ruptured septum
III. Hypotension: BP of 90 Systolic or lower w/o signs of Peripheral Vasoconstriction	27	4		
IV. Shock: Hypotension w/signs of Peripheral Vasoconstriction	11	9	(2) (1) (1) (1)	Anterior and inferior infarct Ruptured ventricle Ruptured septum Acute hemorrhage, l. circumflex
V. Pericardial Friction Rub	7	2	(1) (1)	Massive infarct, left vent. and septum Ruptured ventricle
VI. Thromboembolism	3	0		
VII. Ventricular Rupture	2	2	(2)	Autopsy confirmed diagnosis

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Silence is the unbearable repartee.—Chesterton

From Mister to Doctor

Of all the branches of medicine with which the medical student is confronted, none is more exciting, none more nerve-racking, sweat-producing, and awe-inspiring than is surgery. Surely, every student looks forward with fear and trepidation to the time when, as a senior, he must scrub, don his mask, cap, gown and gloves and stand with the surgical chief at the operating table. . . You perspire, the nose itches, one arm falls asleep, don't dare move now! A Bleeder! A hemostat to the chief! "No not the scissors!" You are in the way—he cracks your fingers—but he dares, for he is the chief. He asks what is this and you sweat, and what is that and you stutter and stammer, can't tell bone from muscle! It's really a nightmare and goes something like this:

10:00 A.M.—Called for first time to assist the chief in surgery.

10:45—Chief entered operating room with a scowl and began to scrub. Pulse jumped to 120.

11:15—Operation began. Assigned a position behind and to the right of the chief. That "knock, knock" noise is from the knees.

11:25—Left leg asleep. Attempted to shift left foot to get relief, thereby kicking the chief in the back of the leg. Received explosive warning for clumsiness. Everyone glared.

11:28—Nose itched. Almost scratched it with sterile glove. Stopped just in time by scowl from friend (?) nurse.

11:30—Couldn't tell chief the name of the nerve that he had picked up. Acidly advised to return to freshman year and study anatomy.

11:33—A bead of perspiration fell from forehead onto sterile drape. Hastily covered by sterile towel by nurse. Bless her! Chief pretended not to see.

11:38—Left leg dead from toes to hip.

11:40—Leaned over to see a structure pointed out by the chief. Anesthetic left leg buckled. Collapsed on chief's right shoulder, causing him to apply his jelly belly to the operative field. Muffled curse came from beneath his mask.

11:40.10—Tried to straighten up but fell off chief's shoulder to the floor, knocking over instrument tray and spot light and sprawled at full length on back, among the buckets and sponges on the floor! Chief straightened up, turned toward me and with a hideous growl grabbed me about the throat, choking me and banging my head against the floor.

11:40.20—"Hey DOC, DOC! Wake up, wake up! You're next to get your diploma." — — THANK GOD!!*

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*Saul, F. William, M.D.: Pink Pills for Pale People, 1949.

Honesty

The teacher asked Johnny if the world was round. He answered, "No."
"Is it flat?"
"No."
"If it isn't round and it isn't flat, what is it?"
"Daddy says it's crooked."

Jacob Braude: Speaker's Encyclopedia

Let's be specific about Campbell's Soups... and *reducing diets*

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Indication—Oral contraception.

Contraindications—Thrombophlebitis, thromboembolic disorders, cerebral apoplexy or a past history of these conditions, markedly impaired liver function, known or suspected carcinoma of the breast, known or suspected estrogen-dependent neoplasia, undiagnosed abnormal genital bleeding.

Warnings—Watch for the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, retinal thrombosis); if present or suspected discontinue the drug immediately.

British studies reported in April 1968[1,2] estimate there is a seven- to tenfold increase in mortality and morbidity due to thromboembolic diseases in women taking oral contraceptives. In these controlled retrospective studies, involving 36 reported deaths and 58 hospitalizations due to "idiopathic" thromboembolism, statistical evaluation indicated that the differences observed between users and non-users were highly significant. The conclusions reached in the studies are summarized in the table below:

Comparison of Mortality and Hospitalization Rates Due to Thromboembolic Disease in Users and Non-Users of Oral Contraceptives in Britain.

Category	Mortality Rates		Hospitalization Rates (Morbidity)
	Age 20-34	Age 35-44	Age 20-44
Users of Oral Contraceptives	1.5/100,000	3.9/100,000	47/100,000
Non-Users	0.2/100,000	0.5/100,000	5/100,000

No comparable studies are yet available in the United States. The British data, especially as they indicate the magnitude of the increased risk to the individual patient, cannot be applied directly to women in other countries in which the incidences of spontaneously occurring thromboembolic disease may differ.

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or sudden onset of proptosis, diplopia or migraine. Withdraw medication if papilledema or retinal vascular lesions are found.

Since the safety of Ovulen in pregnancy has not been demonstrated, it is recommended that pregnancy be ruled out for any patient who has missed two consecutive periods before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule the possibility of pregnancy should be considered at the first missed period.

A small fraction of the hormone agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

Precautions—Pretreatment physical examination should include special reference to the breasts and pelvic organs, and a Papanicolaou smear.

Endocrine and possibly liver function tests may be affected by Ovulen. Therefore, it is recommended that such tests if abnormal be repeated after the drug has been withdrawn for two months.

Pre-existing uterine fibromyomas may increase in size under the influence of progestogen-estrogen preparations.

Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.

In breakthrough bleeding, and all irregular vaginal bleeding, consider nonfunctional causes. Adequate diagnostic measures are indicated in undiagnosed vaginal bleeding.

Carefully observe patients with a history of psychic depression and discontinue the drug if severe depression recurs.

Any possible influence of prolonged Ovulen therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study.

A decrease in glucose tolerance has occurred in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be observed carefully while receiving Ovulen.

Because of the effects of estrogens on epiphyseal closure Ovulen should be used judiciously in young patients in whom bone growth is not complete.

The age of the patient constitutes no absolute limiting factor, although Ovulen therapy may mask the onset of the climacteric.

The pathologist should be informed of Ovulen therapy when relevant specimens are submitted.

Adverse Reactions—A statistically significant association has been shown between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: cerebrovascular accidents, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, breast changes (tenderness, enlargement, secretion), change in weight, changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post partum, cholestatic jaundice, migraine, allergic rash, rise in blood pressure in susceptible individuals, mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme and nodosum, hemorrhagic eruption, itching.

The following laboratory results may be altered by oral contraceptives: hepatic function: increased sulfobromophthalein and other tests; coagulation tests: increase in prothrombin, Factors VII, VIII, IX and X; thyroid function: increase in PBI and butanol extractable protein bound iodine, and decrease in T^3 uptake values; metyrapone test; pregnanediol determination.

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Before prescribing see Detailed Product Information.

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Contraindications: Severe central nervous system depression, comatose states from any cause, hypertensive or hypotensive heart disease of extreme degree.

Warnings: Administer cautiously to patients who have previously exhibited a hypersensitivity reaction (e.g., blood dyscrasias, jaundice) to phenothiazines. Phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides. During pregnancy, administer only when necessary.

Precautions: There have been infrequent reports of leukopenia and/or agranulocytosis and convulsive seizures. In epileptic patients, anticonvulsant medication should also be maintained. Pigmentary retinopathy may be avoided by remaining within the recommended limits of dosage. Administer cautiously to patients participating in activities requiring complete mental alertness (e.g., driving). Orthostatic hypotension is more common in females than in males. Do not use epinephrine in treating drug-induced hypotension. Daily doses in excess of 300 mg. should be used only in severe neuropsychiatric conditions.

Adverse Reactions: *Central Nervous System*—Drowsiness, especially with large doses, early in treatment; infrequently, pseudoparkinsonism and other extrapyramidal symptoms; nocturnal confusion, hyperactivity, lethargy, psychotic reactions, restlessness, and headache. *Autonomic Nervous System*—Dryness of mouth, blurred vision, constipation, nausea, vomiting, diarrhea, nasal stuffiness, and pallor. *Endocrine System*—Galactorrhea, breast engorgement, amenorrhea, inhibition of ejaculation, and peripheral edema. *Skin*—Dermatitis and skin eruptions of the urticarial type, photosensitivity. *Cardiovascular System*—Changes in the terminal portion of the electrocardiogram have been observed in some patients receiving the phenothiazine tranquilizers, including Mellaril (thioridazine hydrochloride). While there is no evidence at present that these changes are in any way precursors of any significant disturbance of cardiac rhythm, several sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients previously showing electrocardiographic changes. The use of periodic electrocardiograms has been proposed but would appear to be of questionable value as a predictive device. *Other*—A single case described as parotid swelling.

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Editorials

The Computers Are Coming, O-ho, O-ho*

MAKE NO MISTAKE about it, the computers are coming. At this moment they are crunching through hospital walls into business offices, laboratories, and right up to the bedside. Fed the correct diet of numbers, these electronic marvels can keep track of the patients' and hospitals' money; digest, store, retrieve, and type out laboratory test results;[1,2] and even take a history,[3] auscultate a heart,[4] and help with physicals.[5]

This march of machines is a welcome one, at least in the laboratory. Properly instructed, computers can make up blood drawing lists for technologists, indicate the amount of blood to draw and the type of tubes and anticoagulants to use; reduce clerical work and minimize recording errors, cull out those tests that have gone awry because of errors or artifacts; flag abnormal results for pathologists and clinicians, calculate normal ranges, spot errors due to faulty methods or instruments, and do it all with blazing speed.

Just how these transistorized subhumans go about their tasks is detailed in part in this issue of MINNESOTA MEDICINE, pages 847 and 853.

From these articles I learned that in nanoseconds† a computer can ingest test results, swallow the information, remember, calculate, store, and then regurgitate the printed results; and I learned that computers fundamentally carry out three jobs: "business data processing, general scientific computing, and real-time, on-line control."

Furthermore, I learned that computers, like people, differ: there are small ones, large ones, cheap ones, expensive ones, slow ones, fast ones, generalized ones, and specialized ones. But unlike people, computers are passive and inflexible. Humans have to spoon-feed them with programmed pabulum: a combination of letters, numbers, punctuation marks, and mathematical symbols.

The problem of conversing with a computer seems to lie in the human mind. Not only do programmers have to nurse computers, but to understand and communicate with them they have to use them in about 2000 special languages; among them, COBOL (Common Business Oriented Language), FORTRAN (Formula Translation), MAD (Michigan Algorithmic Decoder), and JOVIAL (Jule's Own Version of the International Algebraic Language).

Computers process information in nondigital form, but their masters do not follow rigid rules when they think, read, or write. Physicians instinctively sense what is important, what to concentrate on, and what to ignore; we grimace, gesticulate, smile, or modulate our voices to drive a point home. The computer can

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*The Campbells Are Coming, O-Ho, O-Ho. A 16th Century Scottish lyric and tune, authors unknown. See page 827.

†See Test Your Word Score Page 759.

Smiles speak louder than words

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only flash its lights.

Yet, in the world of numbers, the computers reign supreme, and clinical laboratories, you no doubt have noticed, produce myriads of numbers. By processing these numbers and relieving technologists and pathologists of statistical and repetitive drudgery, computers ought to liberate mind power for more creative and thoughtful things—such as interpreting what the numbers mean.

Richard L. Reece. M.D.
Minneapolis, Minnesota

"Worms"

THIS CASE REPORT by Drs. Carlson and Zinneman is excellent not only because of their skill in presentation and documentation but also for the educational service it renders in alerting the medical practitioner to the problems of those returning from military service or from other foreign travel.

There is a need for recognition of the parasitic diseases associated with worms and for enlightenment on the problem of "worms," so aptly described by the late Professor Asa C. Chandler when he wrote: "The name 'worm' is an indefinite though suggestive term popularly applied to any elongated creeping thing that is not obviously something else."

In this age of rapid transit via jet aircraft, one can become infected with a number of parasitic diseases but not present symptoms until some time after one returns to his home locale and his local physician. Outstanding among these parasitic diseases are malaria and the additional examples provided by Drs. Carlson and Zinneman.

Constant awareness of the possibilities for infection by various parasitic forms is increasingly required of the medical practitioner, and this case report is a worthy contribution toward that awareness. Awareness of the possibilities, however, is not sufficient. The practitioner must have some background knowledge of the life cycles of these parasitic organisms and the various approaches to diagnosis, treatment, and eradication from the host.

The real problem is one of education and of sufficient emphasis on parasitic diseases. The subject of parasitism is generally relegated to showing a few typical slides and the sincere hope that the student will eventually look through a textbook. The concept of parasitism can and should be taught in the very beginning of a youngster's contact with the subject of animal and plant biology. From this point on, the emphasis needs to be on enlargement of the concept, and this should progress with as much firsthand experience as possible until, when in medical school, the student is ready and able to correlate organisms with disease processes and their diagnosis and treatment.

There are a number of approaches to supplying the firsthand experience mentioned above. One is to utilize, as demonstration material, specimens taken from animals housed in the medical school's animal colony or to maintain (as teaching material) animals which harbor such blood forms as malaria, the various filarial worms, and trypanosomes. The life cycles of typical protozoan forms can be readily demonstrated in fecal samples from mice, rats, guinea pigs, and other laboratory animals; and many typical helminths can be found in common laboratory animals.

There is nothing quite so dead, or deadly, from an educational standpoint, as a slide of a fixed and stained organism—especially when this organism or a comparable animal form could be shown alive and moving about in a microscopic field! The experience of seeing and discussing the live organism enhances the whole educational process and cannot be overemphasized. Obviously, care must be exercised if any of these organisms are potential human pathogens. In fact, the whole subject of zoonotic infections—those suffered primarily by animals other than man but secondarily transmissible to man—is poorly treated. Our knowledge of host specificity and ranges is broadening within the field of animal parasitology, but this knowledge needs to reach further into the realms of medical and veterinary education.

It is realized that those of us in specialty areas such as medical parasitology have a ten-

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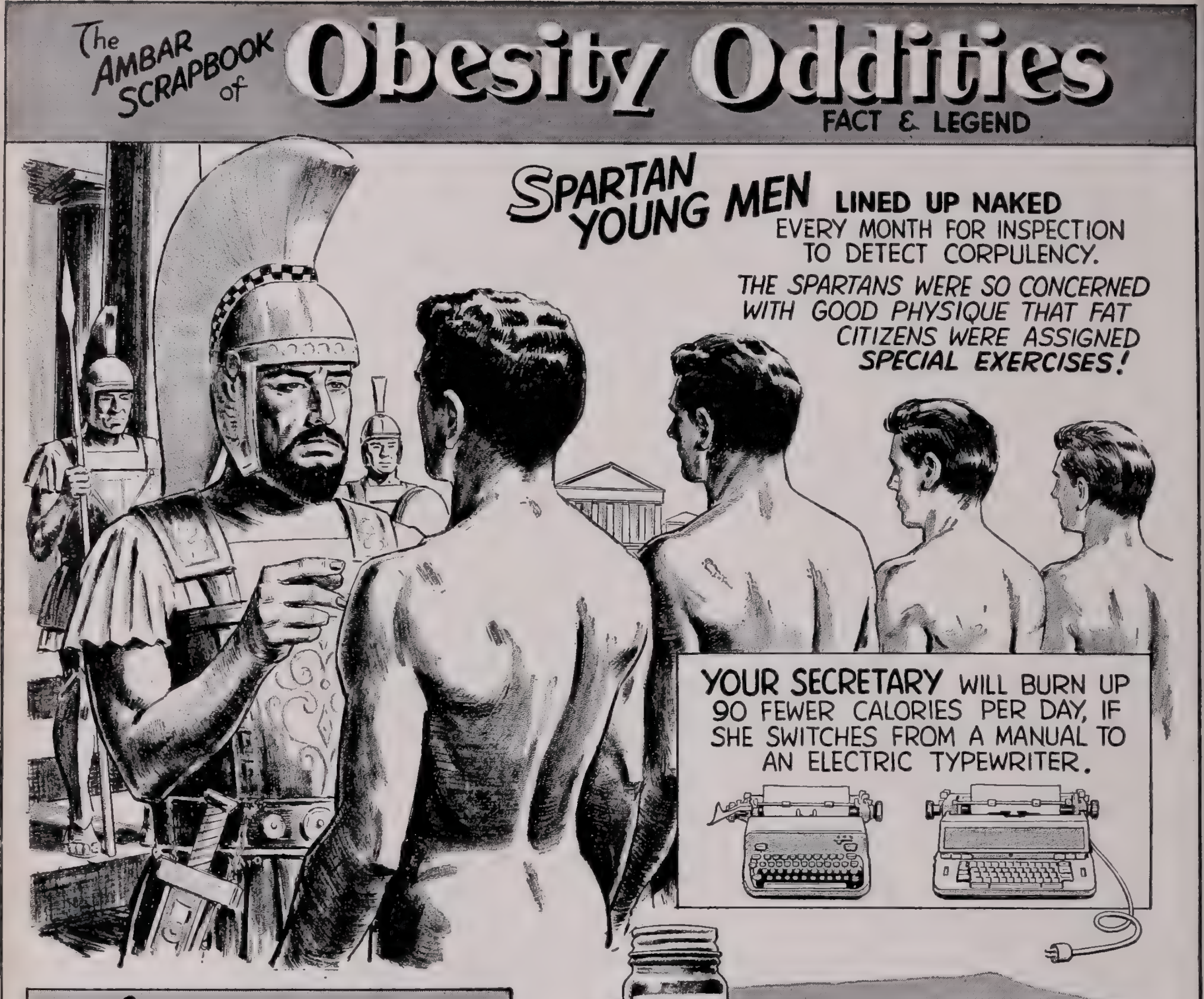
*Carlson, David, and Zinneman, Horace H.: Ascariasis. Minnesota Med 51:1713, 1968.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dency to demand emphasis on our particular field in the educational program. However, it must be realized also that the demands made on the general practitioner are increasingly those of these very areas of specialization. It is to be hoped that, with the creation of Health Science Centers and Community Health Programs, this needed broadening of the educational base may be attained and constantly maintained—even between wars. In the meantime, the appearance of articles such as this one by Drs. Carlson and Zinneman is of genuine educational benefit to all.

John H. Thompson, Jr., Ph.D.*
Rochester, Minnesota

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*Section of Clinical Pathology, Mayo Clinic.

Vascular Fistulas of the Dura*

WITH A VASCULAR FISTULA of the dura, the most common presenting symptom is a bruit which the patient complains of and which frequently can be heard with a stethoscope. Because the fistula is most commonly between the middle meningeal artery and a nearby dural sinus, the bruit is heard best over the ear and side of the head rather than over the eye and orbit, as it is with a carotid cavernous fistula. Another common presenting complaint is focal headache, usually localized over the area of the fistula. With a fistula which occurs spontaneously, the headache is frequently of sudden onset and, after it appears, persists.

If the fistula is located along the base of the skull, the predominant drainage is into the petrosal or cavernous sinus. A fistula from the meningeal branches of the external carotid artery to the cavernous sinus causes proptosis,† conjunctival injection, blurring of vision, and extraocular nerve palsies as seen with a carotid cavernous fistula. If the fistula is located more distally in the course of the middle meningeal artery, it may drain into the superior sagittal sinus. Direct transmission of the arterial pressure to the venous sinuses may increase the intracranial pressure and give rise to the type of picture described in Huber and Joos's first case.

I have recently seen one patient in whom a fistula developed between the meningeal branch of the anterior ethmoidal artery and the dural sinuses over the anterior portion of the cranial fossa. This patient experienced sudden onset of pain above the left eye, which mimicked trigeminal neuralgia. Fistulas of this type may also give rise to focal cortical disturbances such as seizures. The mechanism for this is transmission of the arterial pressure into the venous sinuses and then retrogradely into the adjacent cortical veins where it causes a focal cortical disturbance. These patients not uncommonly have learned that pressure over the carotid artery will relieve their bruit and headache.

Rupture of this type of fistula may give rise to spontaneously occurring subdural and epidural hematomas. Although these fistulas, especially those of traumatic origin, may thrombose spontaneously, more frequently they require surgical therapy. Ligation of the external carotid artery is a frequently used method of treatment. When this method has failed or does not seem reasonable, the fistula is approached directly by craniotomy with excision of the dura containing the fistula or direct ligation of the middle meningeal artery.

Albert L. Rhoton, Jr., M.D.
Rochester, Minnesota

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*Huber, P., and Joos, F.: Vascular Malformation of the Dura Mater. Minnesota Med 52:157, 1969.

†See Test Your Word Score Page 759.

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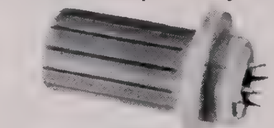

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Dog-Bite Wounds Should be Considered Tetanus Prone*

IN THE MARCH ISSUE of MINNESOTA MEDICINE,* Col. George H. Chambers and Major John F. Payne report their unique and interesting experience in the treatment of patients with dog-bite wounds. They conclude that such wounds, when significant, must be viewed as "infected crush wounds" rather than mere puncture wounds and are best managed by thorough cleansing, splinting, bulk dressings, elevation, and the use of soaks. Secondary closure and split-thickness skin grafting can be performed later if the wound does not close satisfactorily by secondary intention.

Possibly, as an oversight, they have omitted the importance of tetanus prophylaxis in such patients. That dog-bite wounds (and other animal bites, including insect bites) are tetanus-prone is supported by several reports in which these wounds were considered the foci of tetanal infections in patients with clinical tetanus.[1-3] In the report by Chambers and Payne, although cultures from the dog-bite wounds did not reveal *Clostridium tetani*, the possibility of this infection cannot be ruled out. Writers on the subject have consistently emphasized the difficulty in isolating these causative organisms from suspected foci of infections in patients *with* clinical tetanus. Even with the best techniques available, isolation of *C. tetani* organisms was successful in less than a third of 119 patients treated at the Mayo Clinic and related hospitals. Furthermore, since the patients reported by Chambers and Payne were members of the United States Armed Forces, they probably were adequately immunized against tetanus, as tetanus toxoid immunization is mandatory in the armed services. Such immunization would have prevented clinical tetanus in any of the patients who may have had tetanal infection complicating a dog-bite wound.

Thus, dog-bite wounds must be considered tetanus-prone and should be treated as such. When the bite is superficial and the wound is minor, careful cleansing, debridement, and proper dressings should be sufficient to prevent tetanus. Active immunization with tetanus toxoid can be started, and completed later, in any patient who has not been previously immunized. If the bite is serious enough to be considered an "infected crush wound," tetanal immunization, in addition to the treatment prescribed by Chambers and Payne, is necessary to prevent this dread disease. If the patient has not been previously immunized with tetanus toxoid, 250 units† of human tetanus hyperimmune globulin (human tetanus antitoxin) should be given intramuscularly when he is admitted to the physician's office or to the emergency room. Currently it is accepted policy to initiate active immunization at the same time. With another syringe and another site, the initial injection of 0.5 ml of mineral-absorbed tetanus toxoid (preferably) is given intramuscularly, and arrangements are made to complete the "basic series" later. This would mean a second injection within four to six weeks and a third injection within another six to 12 months. Dual injections of human tetanus antitoxin and tetanus toxoid (with completion of the basic series as prescribed) produce passive immunization that is prompt and effective and active immunization that is long-lasting and continuous.[5]

For the patient who has a significant dog-bite wound and who has been previously and appropriately immunized with tetanus toxoid (as can be assumed to have been true of all patients reported by the authors), in accordance with the guidelines for the medical profession regarding tetanus prevention as outlined at the International Conference on Tetanus[6] held in Bern, Switzerland, in 1966, a "wound booster" of 0.5 ml of tetanus toxoid is recommended if the interval since the "basic series" or a subsequent booster has been longer than one year.

It is my opinion that, with an immunologic agent as effective and dependable as tetanus toxoid, we can now eliminate the use of the "wound booster." Available evidence supports the impression that any patient who has re-

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*Chambers, G. H., and Payne, J. F.: Treatment of Dog-Bite Wounds. Minnesota Med 52:427, 1969.

†If the wounds are extensive and severely infected, 500 units are suggested.[4]

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ceived the "basic series of tetanus toxoid" and an "interval reinforcement booster" of toxoid every five years thereafter can be considered continuously and adequately protected against tetanus during the five-year period. Admittedly, the considered five-year "safe interval" is arbitrary, and further experience and observations may lengthen this interval.[7] In the meantime, if the general plan of tetanus toxoid immunization as proposed is accepted and implemented, physicians, when treating patients who have contaminated wounds (including dog bites), could do as the authors did, namely, direct their full attention to the local care of these wounds without concern about tetanus.

Norman A. Christensen, M.D.*
Rochester, Minnesota

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*Section of Internal Medicine, Mayo Clinic.

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Test Your Word Score

Endotracheal—*within the trachea* (page 719).

Prodromal—*premonitory* (page 722).

Adrenergic—*relating to nerve fibers that liberate sympathy* (page 726).

Supravital—*pertaining to the staining of living tissues or cells after removal from a living body* (page 732).

Colpocytology—*vaginal cell study* (page 733).

Microglial—*pertaining to material consisting of small adventitious cells scattered within the nervous system* (page 738).

Taxonomy—*classification of* (page 741).

Nanosecond—*one billionth of a second* (page 751).

Proptosis—*protrusion of the eye* (page 755).

Erythropoiesis—*formation of red cells* (page 821).

Everybody wants to be somebody: nobody wants to grow—Goethe

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Letter to the Editor

I cannot refrain from commenting on the article by Drs. Kiser, Peterson, and Johnson entitled "Open Heart Surgery in Elderly Patients," which was in the February 1969 issue of MINNESOTA MEDICINE.*

It certainly is of note that the four elderly patients reported in the article survived their operative procedures. In order to put this report in proper perspective, however, I believe there are three questions that should be answered. These are as follows:

1. What has been the long-term survival of these four patients?
2. How many other patients in this same age group have been operated on and have not survived surgery?
3. What are the objective data indicating hemodynamic improvement in these people?

Since each of the patients reported had heart catheterization preoperatively, it would be most useful to know more about the preoperative hemodynamic data than what was included in the report. A final bit of very useful information would be some statement as to the therapeutic programs these patients were following before their open heart surgery.

Paul Winchell, M.D.†
Minneapolis, Minnesota

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*See page 231.
†Associate Professor, Department of Medicine, University of Minnesota.

In response to the questions raised by Dr. Paul Winchell regarding the article "Open Heart Surgery in Elderly Patients," the four patients reported were the *only* patients operated upon in this seventy to eighty age group at the time this report was submitted. Since that time, three other "eighth-decade" patients have undergone surgery for aortic valve replacement with one operative death. Of those patients reported in the article, the long-term survival has been 36 months, 16 months, 18 months and 12 months.

One of these patients expired during the recent "flu" epidemic of viral pneumonia when 16 months postoperative. Up until the time of his death, he was not limited by cardiac disease. An autopsy was performed and revealed no evidence of thrombosis, embolism, congestive heart failure or malfunction of the prosthesis. The remainder of the patients are presently living and functioning at an improved level.

The objective data to indicate hemodynamic improvement consists of absence of the previous clinical evidence of hemodynamic derangement and elevation of their functional classification. All of these patients, except one, were functional Class IV, and they were being treated with digitalis, diuretics and salt restriction.

In the interest of brevity, only that catheterization data thought to be relevant was included in the report. Indeed, there is some question whether cardiac catheterization is an absolute necessity prior to surgery in any of these patients.

Joseph C. Kiser, M.D,
Minneapolis, Minnesota

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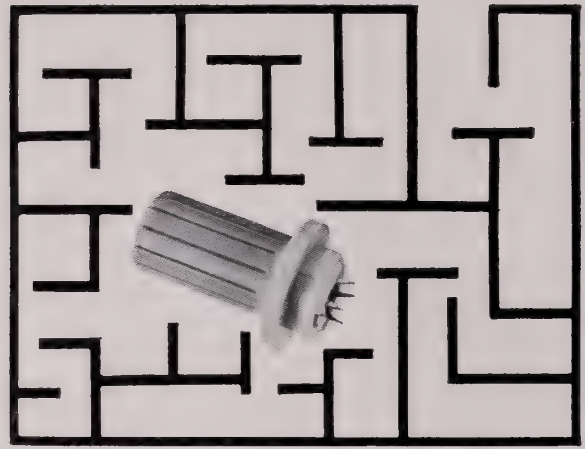

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The Editor's Soliloquy

Purism

ALL OF US ARE M.D.'s and can qualify as experts in the field of medicine. From that vantage point we are fully competent to obtain a history, do a complete examination, make an evaluation, offer a diagnosis, and recommend treatment. How else can the doctor know what he is referring; or the patient know whom she needs to see, without the privilege of consulting the physician of her choice? Beyond that some of us may further qualify as specialists; but since that does not and should not remove us from the category of having a knowledge of general medicine, we need not assume the guise of purism in the staff room and practice something else in the office.

Some of my colleagues may proclaim in the hospital staff room such strict adherence to their specialty that they will accede to nothing but "cut and sew." To exceed that, they maintain, infringes on the private domain of the referring physician, the examining doctor, the diagnostician, or the laboratorian.

They may examine the area where they plan to cut, but a pelvic examination, for example, is in the realm of the gynecologist; the heart belongs to the cardiologist; the lungs are the pneumologist's forte. For the aching back consult the orthopedist; for the creaking joints, the rheumatologist; for the ingrown toenail, the podiatrist. If red blood cells appear in the urine, see the urologist; for a trace of sugar in the urine confer with the diabetologist. It may become poltroon.

Within the sanctuary of their private offices, however, some professional purists may prescribe for a case of walking pneumonia; give a tranquilizing pill or two for the jitters, some sleeping pills for insomnia, an antacid for dyspepsia, a gargle for a sore throat, a salve for dermatitis, or maybe even a flu shot. Or they may conceivably go so far as to cavalierly recommend a six-week holiday away from the nagging spouse—to avoid a nervous breakdown: a better ploy than seeing a psychiatrist—and cheaper!

On the other hand, the non-surgical specialist may apply a butterfly dressing for a laceration (provided it doesn't exceed an inch or two), a medically-treated bandage for a sprain, a plaster for a lumbago back, or he may even presume to watch or give a hormone shot for a lump that shouldn't be there.

Medicine is a humanitarian profession wherein protocol should not be so rigid that the specialist cannot ethically double as an adviser on simple medical problems when the need arises—for the convenience and reassurance of the patient. Despite progressively narrowing specialization, boundaries should always remain flexible. For a specialist to step outside his specific province on occasion is creditable; but to disavow doing so is hypocritical.

Carl O. Rice, M.D.

Old Doc Hess says: For the man who believes in it, euthanasia is a method of salving the conscience and alleviating the remorse of the survivors.—COR

Civilization is simply a series of victories over nature.—William Harvey

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ANSWER: Controversy exists as to whether rectal carcinoids have malignant potential. There is little justification for such doubts, however, since cases have been reported showing indisputable evidence of malignant changes, and in some cases metastases have been demonstrated. Nevertheless, foregut and hindgut carcinoids are usually benign, histologically and biochemically, as opposed to carcinoids of the ileum which frequently take on malignant characteristics and exhibit the carcinoid syndrome.

Size seems to be an important factor as to malignant potential in rectal carcinoids. When less than 1.0 cm. in size such tumors may be treated as benign, and local excision can be considered adequate. In lesions measuring more than 2.0 cm., radical surgery should be considered. Because of its small size and the fact that all the tumor in the instant case was removed, treatment can be considered sufficient. The patient should be followed by periodic proctoscopic examinations, however, and if local recurrence occurs more radical surgery should be considered.

Harold D. Kletschka, M.D.
Montgomery, Alabama

A pessimist is a man who has been compelled to live with an optimist.—E. Hubbard

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The greatest of faults, I should say, is to be conscious of none.—Carlyle

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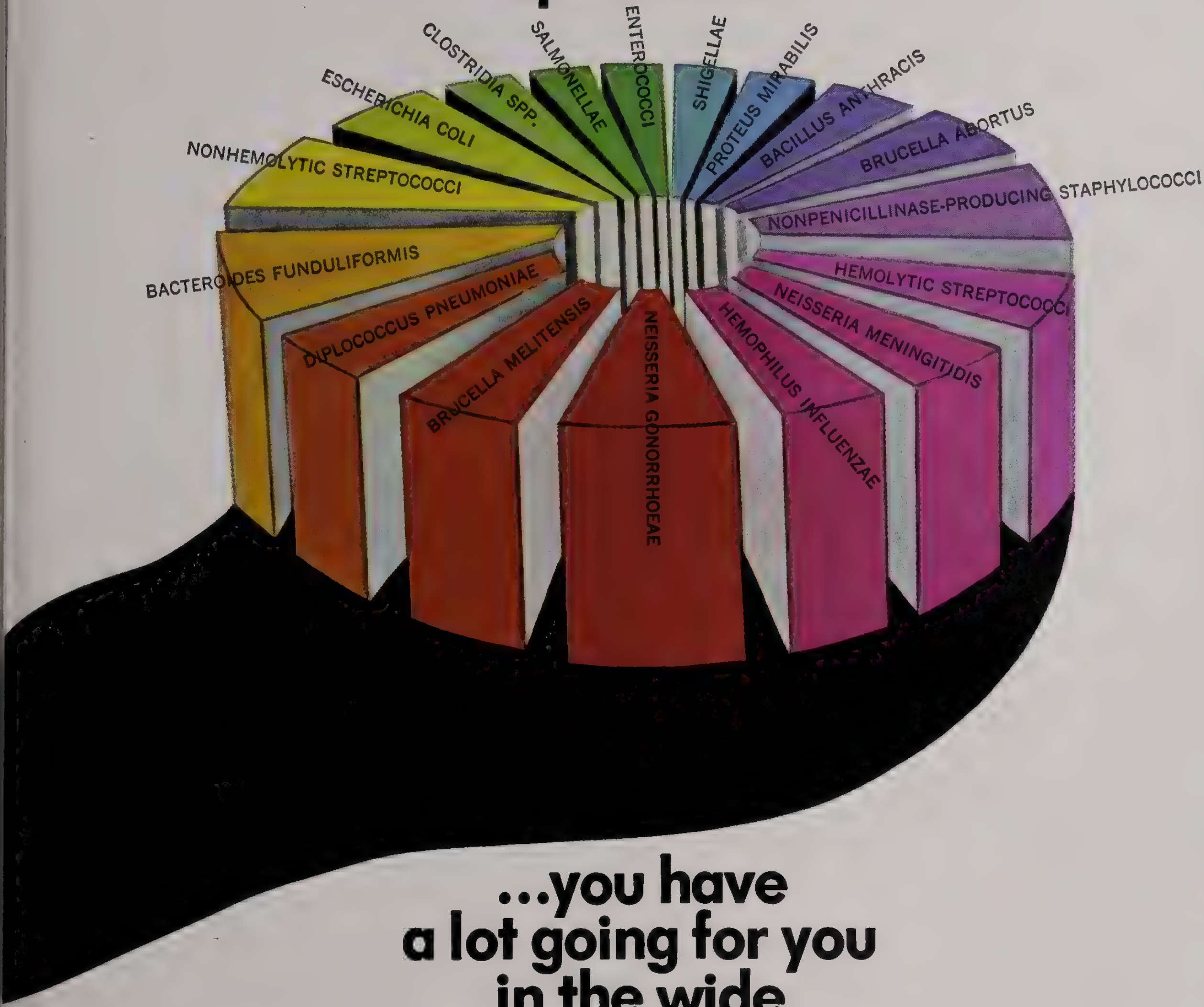
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When stress is situational—environmental pressure, worry over illness—the treatment often calls for an anxiety-allaying agent which has a prompt and predictable calming action and is remarkably well tolerated. Butisol Sodium (sodium butabarbital) meets this therapeutic need.

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Adverse Reactions: Drowsiness at daytime sedative dose levels, skin rashes, "hangover" and systemic disturbances are seldom seen.

Warning: May be habit forming.

Usual Adult Dosage: As a daytime sedative, 15 mg. (¼ gr.) to 30 mg. (½ gr.) t.i.d. or q.i.d.

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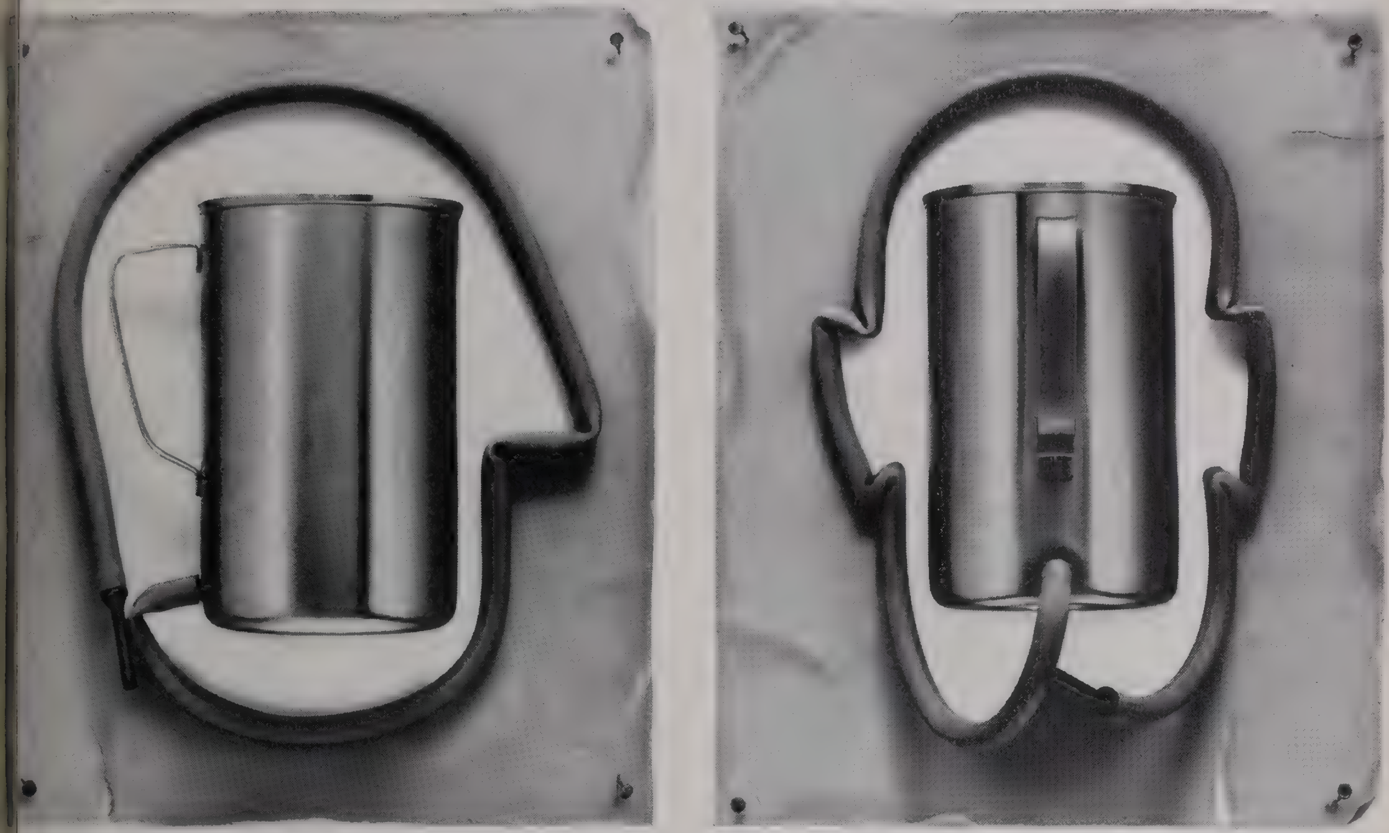
BUTICAPS® [Capsules Butisol Sodium (sodium butabarbital)] 15 mg. (¼ gr.), 30 mg. (½ gr.).

McNEIL

McNeil Laboratories, Inc., Fort Washington, Pa.

Public Enema No.1



Caim the rewards of sparing your patients the tubes ad tribulations of unpleasant enemas.

Cmpared to enemas, Dulcolax suppositories are a gntler and simpler way to empty the bowel. Gone ae the tubing, the "accidents", and the bruised egos. Jst one suppository, inserted against the bowel wall, uually brings about an evacuation within 15 minutes to an hour.

In the hospital, order Dulcolax for constipation or bowel cleansing. Your patients will often prefer it to embarrassing enemas. And you can be sure nurses will appreciate the saving in time and effort.

Dulcolax tablets taken at night usually result in a bowel movement the following morning. A combination of tablets at night and a suppository the next morning generally cleans the bowel thoroughly in preparation for surgery or special procedures. Keep in mind, however, that the drug is contraindicated in the acute surgical abdomen.

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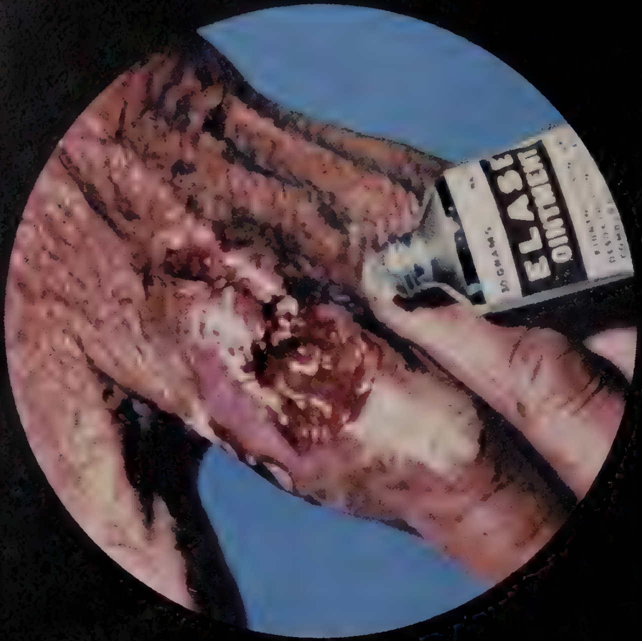
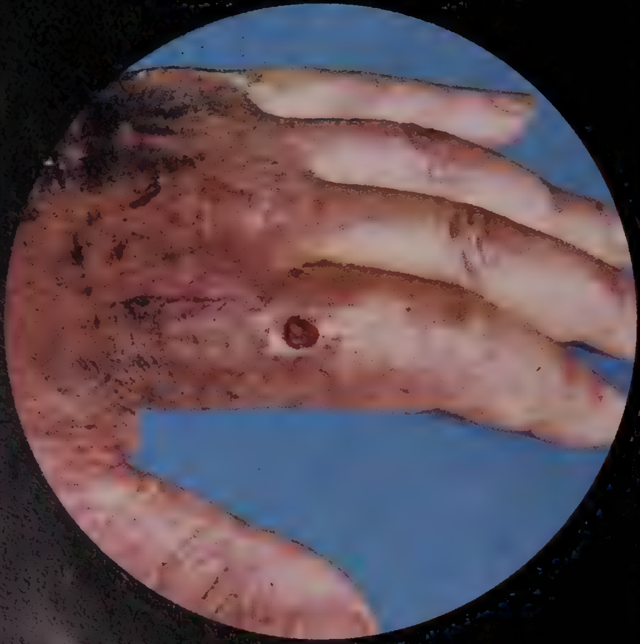
DU-6118

this ulcer did not heal...until its surface was cleared of dead tissue and debris



FIRST APPLICATION
ELASE Ointment is applied to a deep ulceration of a finger.

EIGHTEEN DAYS LATER
Healing has progressed rapidly without interruption or interference from any accumulated purulence or necrotic tissue. Greatly reduced size of lesion and minimal scar tissue indicate quality and vigor of healing which is almost complete.



to aid in debridement
to facilitate healing
in chronic cutaneous ulcers...

Elase® Ointment

(fibrinolysin and desoxyribonuclease, combined, [bovine] ointment)

PARKE-DAVIS

By helping to remove dead tissue and debris from the ulcer's surface, ELASE Ointment creates a better environment for the elimination of infection, for healthy granulation... *for healing.* Its lytic enzymes effectively break down DNA in dead leukocytes and other debris... the fibrin in blood clots, serum, and purulent exudates... and the denatured proteins in necrotic tissue. Protein elements of *living* tissue are relatively unaffected. ELASE Ointment is indicated in stasis ulcers and in other infected or inflamed ulcers caused by circulatory disturbances. In cases requiring skin grafting, it is used preoperatively for debridement. For ambulatory patients debridement with ELASE Ointment is a convenient therapy and a regimen likely to be followed. *Precautions:* Observe usual precautions against allergic reactions, particularly in persons with a history of sensitivity to materials of bovine origin or to mercury compounds. *Adverse Reactions:* Side effects attributable to the enzymes have not been a problem at the dose and for the indications recommended. *Discussion:* Successful use of enzymatic debridement depends on several factors: (1) dense, dry eschar, if present, should be removed surgically before enzymatic debridement is attempted; (2) the enzyme must be in constant contact with the substrate; (3) accumulated necrotic debris must be periodically removed; (4) the enzyme must be replenished at least once daily; and (5) secondary closure or skin grafting must be employed as soon as possible after optimal debridement has been attained. It is further essential that wound-dressing techniques be performed carefully under aseptic conditions and that appropriate systemically acting antibiotics be administered concomitantly if, in the opinion of the physician, they are indicated. *Available:* ELASE Ointment is supplied in 30-Gm. tubes containing 30 units (Loomis) of fibrinolysin and 20,000 units of desoxyribonuclease with 0.12 mg. thimerosal (mercury derivative); and in 10-Gm. tubes containing 10 units of fibrinolysin and 6,666 units of desoxyribonuclease with 0.04 mg. thimerosal. ELASE Ointment has a special base of liquid petrolatum and polyethylene; contains sodium chloride and sucrose used during manufacture; is stable at room temperature through the expiration date stated on the package.

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PARKE-DAVIS

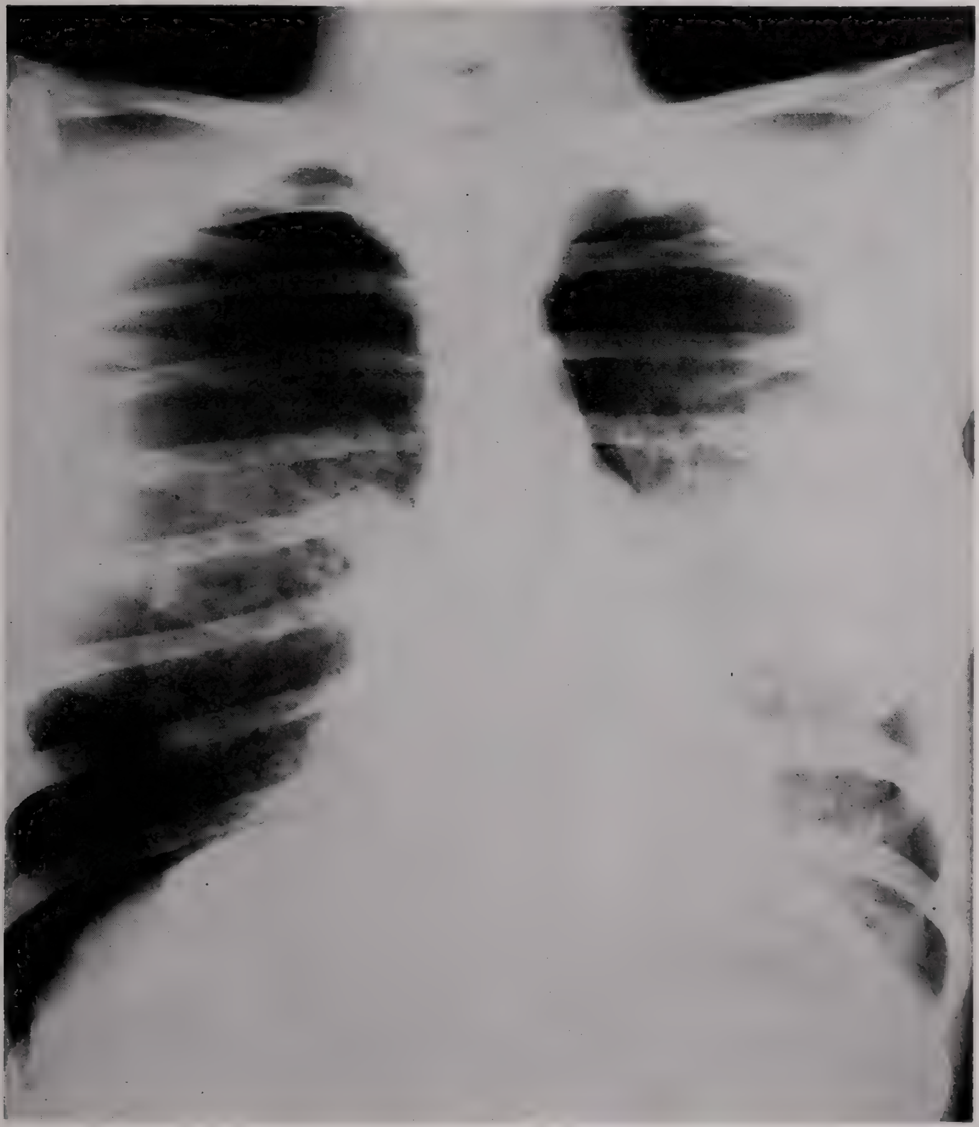
48168

The Viewing Box

Dyspnea in a Teen-age Girl

THIS 13-YEAR-OLD school girl complained of moderate dyspnea and dry cough. She had been feeling generally ill for several days. On examination, scattered skin lesions were present on the head and neck, described as healing vesicles. WBC was 14,000. There was no fever. The chest x-ray taken on admission is shown (Figure).

What is your diagnosis? (See next page.)



Figure

Diagnosis: Pulmonary histiocytosis with spontaneous pneumothorax.

Clinical Course

The bilateral spontaneous pneumothorax was readily apparent. Chest tubes were inserted bilaterally, but the pneumothorax proved difficult to manage. It recurred and replacement of tubes was required several times. Lung fields consistently showed a fine granular infiltration and a cystic appearance.

About four weeks after admission, left thoracotomy was done and the left lung biopsied. The lung was grossly abnormal in appearance during the surgical procedure, and several subpleural cysts were seen to rupture spontaneously while the lung was under observation. The histological diagnosis of the lung tissue was histiocytosis; skin tissue from the neck lesions showed similar abnormalities.

Discussion

Eosinophilic granuloma, Hand-Schueller-Christian and Letterer-Siwe syndromes are older terms designating portions of the spectrum of diseases included under the more general term, histiocytosis. These diseases are seen most commonly in white children in the first decade of life; the most severe form of the disease, Letterer-Siwe syndrome, in the first year of life. Skeletal involvement may be the only manifestation of histiocytosis (eosinophilic granuloma), and overall, bony lesions are present in 80% of the cases.[1]

Pulmonary histiocytosis is usually associated with widely disseminated disease, but a few cases of what appear to be primary pulmonary histiocytosis have been described.[2] These have tended to be in adults, usually in males. Several patients have presented with spontaneous pneumothorax.

The outlook for patients with pulmonary histiocytosis is extremely variable, but generally quite prolonged. The pulmonary form can result in fibrotic changes and chronic pulmonary disability.

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Safety

The curfew tolls the knell of parting day;
A line of cars winds slowly o'er the lea;
A pedestrian plods his absent-minded way
And leaves the world quite unexpectedly.

Inside the Circle

Tongue Twisters

There are those awful things in medicine—adiposis dolorosa mesenterica, phlegmasia alba dolens, and subluxation of the sacroiliac synchondrosis.—Osler

Obstetrics and Gynecology Seminar

Induction of Labor by Intra-amniotic Injection of Hypertonic Solutions*

INJECTION OF HYPERTONIC SOLUTIONS into the amniotic cavity is not a new technique for induction of labor. While studying the problem of induction in cases of therapeutic abortion, fetal death in utero, or potentially lethal fetal anomalies, Aburel[1] discovered that the injection of 33% saline was an effective means of terminating the pregnancy. Boero[2] was impressed by the clinical observation that, when pregnancy was complicated by a serious medical condition such as tuberculosis or heart disease, spontaneous death of the fetus frequently led to improvement in the mother's condition. Therefore, as a method for terminating fetal life, he used injection of 2 to 3 ml of formalin into the amniotic fluid. At about the same time, Burke[3] noted that labor was frequently induced when radiopaque contrast medium was injected in attempts to diagnose placenta praevia by amniography. Subsequently, Playfair[4] used this same method to induce labor in 115 normal-term pregnancies with very poor results; induction occurred in all but four of these patients, but there were 16 fetal deaths and one maternal death. Playfair (cited by Fuchs[1]) later reported injection of 50% glucose solution into the amniotic cavity.

In 1948, while trying to find a simpler method of inducing labor in cases of fetal death in utero, Portes and associates[5] discovered that simply distending the uterus with isotonic saline was frequently effective. The intra-amniotic injection of hypertonic saline for induction of labor became widely used in Japan after legalization of abortion there in 1948. However, between 1948 and 1950 at least 25 maternal deaths in Japan were attributed to this technique, and the complication rate following its use was stated to be 50%.[6] These poor results were attributed by Wagatsuma[6] to use of the method by inadequately trained persons and to poor selection of patients. The experiences of the Japanese with hypertonic saline essentially stopped all further progress with this technique for the next 10 to 15 years.

By the late 1950s and early 1960s, active surgical management was the primary form of treatment for therapeutic or legal middle-trimester abortion, as well as for the management of missed abortion. The rebirth of interest in the hypertonic saline method for induction of labor and its eventual clinical application began in 1962. At that time, Bengtsson and Csapo[7] used this method to suppress placental formation of progesterone in an effort to verify Csapo's[8] theory of progesterone block control of the pregnant uterus.

Procedure

Transvaginal

The hypertonic solution can be injected either transvaginally or transabdominally. The transvaginal route is recommended by some for pregnancies of 13 to 20 weeks' gestation, whereas the abdominal approach is preferred in more advanced pregnancies. For the vaginal approach, the unanesthetized patient is placed in the lithotomy position and then prepared and draped as for any vaginal procedure. The bladder is emptied prior to further instrumentation. The cervix is then pulled down, and an appropriate needle is inserted through the anterior wall of the cervix just below the junction with the bladder so that the needle forms an angle of 15 to 20° with the axis of the cervix. When free flow of amniotic fluid through the needle has been established, as much fluid as possible is allowed to escape before the hypertonic solution is injected.

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*This paper was prepared under the supervision of members of the faculty of the Mayo Graduate School of Medicine.

Transabdominal

When the transabdominal route is used, the patient is placed in the supine position and the abdomen is prepared and draped as for laparotomy. The procedure is then similar to that of amniocentesis, with use of local anesthesia in the form of a skin wheal through which the needle is inserted in the midline halfway between the symphysis and the fundus of the uterus. Again, the amniotic fluid is withdrawn before injection of the hypertonic solution.

General Principles

Certain general principles in the performance of this procedure, whether via the vaginal or the abdominal route, should be stressed. First, strict adherence to sterile technique is mandatory. Second, most investigators currently prefer to use 20% sodium chloride solution for intra-amniotic injection; the use of 50% glucose for induction of labor is not as acceptable because of the greater likelihood of infection with this material. Third, the amount of hypertonic solution injected into the amniotic cavity should be equal to the volume of amniotic fluid removed, up to a maximum of 200 ml. Fourth, it is advantageous to know the approximate amount of amniotic fluid present at various early stages of pregnancy. Wagner and Fuchs[9] derived a formula which provides such an approximation: the average volume of amniotic fluid at 15 weeks' gestation is 125 ml; for each week prior to 15 weeks, down to 11 weeks, subtract 25 ml; for each week after 15 weeks, add 50 ml. Fifth, the patient should be fully awake during the procedure in order to be able to report any unusual symptoms such as pain, dizziness, marked thirst, or sudden sensation of heat in the upper part of the body which would suggest intramyometrial or intravascular injection. The injection itself should be performed slowly, at a rate of 2 to 4 ml/min. Finally, this procedure should be used only in obstetrical units and should be performed by competent experienced personnel.

Evaluation of Method

The basic clinical studies of this technique were done by Bengtsson and Csapo[7] using two different groups of patients—normal middle-trimester patients who were to have legal abortions, and patients with fetal deaths in utero or missed abortions.

In the middle-trimester patients undergoing legal abortions, the following results were obtained. Prior to the intra-amniotic injection of hypertonic saline, the base-line active pressure of the uterus was very low, averaging 4 mm Hg. During the first three hours after the injection, when the induced hypertonicity was maximal, the average increase in active uterine pressure was only 2 mm Hg. Likewise, no significant increase in uterine activity was noted during this time. By 16 to 22 hours after the injection, when the induced hypertonicity had diminished to an insignificant level, the intra-amniotic pressure had reached an average value of 30 mm Hg. The process of evolution of uterine activity was partially completed by 16 to 22 hours after injection, as indicated by detectable changes in the cervix. However, further evolution of uterine activity was required for clinical progress, as indicated by the fact that the average time from injection to abortion was 34 ± 5 hours.

The peak intra-amniotic pressures recorded after injection of hypertonic saline were in the range of 60 to 90 mm Hg, which are comparable to or greater than the pressures recorded during normal labor at term. On the other hand, the same maximal working capacity of the uterus could not be achieved in normal middle-trimester pregnancies by using oxytocin alone, even though the infusion rates were unlimited. Once clinical labor began after injection of hypertonic saline, it was of surprisingly short duration, usually two to three hours until abortion occurred. Interestingly enough, it has been established[7] and confirmed[10] that the time from injection to abortion can not be shortened by the administration of oxytocin. This is thought to be due to the fact that the hypertonic solution has already elicited the maximal working capacity of the uterus and, therefore, the addition of oxytocin stimulation produces no further effect. On the other hand, the systemic administration of progesterone appears to delay the process of evolution of uterine activity and thereby prolong the injection-to-abortion interval.

In the group of patients with fetal deaths in utero or missed abortions, development of uterine activity occurred more rapidly. The injection-to-abortion interval averaged 13.5 hours. However, the process of evolution of uterine activity went through the same pattern of development in both groups—namely, a delayed, gradual change from local, nonpropagating, asynchronous uterine activity to a stage of synchronous, propagative uterine activity. The addition of oxytocin stimulation in this group of patients also did not shorten the injection-to-abortion interval.

TABLE

Summary of Reported Results of Intra-amniotic Injection of Hypertonic Solution for Induction of Labor

Investigators	No. of patients	Latent period (hr)		Active labor (hr)	Success rate (%)
		In patients with therapeutic abortions			
Bengtsson and Csapo[7]	30		33*		100
Wagner and associates[10]	239		36.5*		94
Gochberg and Reid[11]	26		36.5*		85
Jaffin and associates[12]	6	21.3		1.8	100
Weingold and associates[13]	27	22.6		2.8	100
Kerr and associates[14]	16	18.3		8.4	75
		In patients with fetal death in utero			
Bengtsson and Csapo[7]	15		14*		100
Jaffin and associates[12]	6	14.3		1.8	100
Weingold and associates[13]	9	18.2		1.3	100
Kerr and associates[14]	9	18.3		8.4	89

*These data are overall injection-to-abortion interval.

In a similar group of patients with fetal death in utero, the use of oxytocin stimulation alone for periods of 14 to 24 hours failed to produce completion of abortion in the majority of cases and clinical progress could not be demonstrated during the infusion period. After the intra-amniotic injection of hypertonic saline there was a uniform pattern of labor consisting of a painless latent period during which cervical effacement occurred, followed by a short, active period of high-intensity contractions which usually resulted in a complete abortion with minimal loss of blood.

The validity of Bengtsson and Csapo's work has been confirmed by other investigations (Table).

Mechanism of Action

Four hypotheses have been advanced to explain this phenomenon:

1. The hypertonic solution alters the morphology of the placenta and thereby affects placental endocrine function and its control over the pregnant uterus.
2. Uterine volume is increased due to alterations in amniotic fluid volume in an attempt to achieve equilibrium with the hypertonic solution.
3. There may be an indirect neuroendocrinologic action produced, which affects the hypothalamus and neurohypophysis, causing an increase in endogenous secretion of antidiuretic hormone and oxytocin.
4. There may be a direct effect of the hypertonic solution on the fetal membranes or myometrium.

A working theory combining the first two of these possible mechanisms is by far the most logical explanation for the effectiveness of this technique. The basis for such an explanation lies in Csapo's[15] development of the progesterone block theory proposed in the 1950s. Csapo and co-workers[16] stated that effective uterine activity was controlled by the ratio of uterine volume to the concentration of progesterone in the myometrium (V/P_m). According to this theory, both uterine volume and placental progesterone concentration increase during normal pregnancy. The pregnancy is maintained as long as the ratio of V/P_m remains small; however, when this ratio reaches a certain critical value, the pregnancy terminates. Furthermore, it is the myometrial progesterone concentration, P_m, which is the "defense mechanism" of pregnancy because of its ability to suppress intrinsic activity and pharmacologic reactivity of the pregnant uterus. Therefore, the effectiveness of intra-amniotic injection of hypertonic solutions for the induction of uterine activity is thought to be due to two actions. First, the uterine volume is increased due to an increase in amniotic fluid volume. Second, the hypertonic solution damages the placental structure, causing a decrease in production and transport of progesterone, resulting in a weakening of the progesterone block or a partial progesterone withdrawal. The result of each of these changes is to increase the ratio V/P_m, which favors the evolution of uterine activity.

Some laboratory data are available to support this hypothesis. With regard to the increase in uterine volume following introduction of hypertonic saline, it has been shown that the volume increases by an average of 25 to 30% within three hours after injection.[17] Gochberg and Reid[11] used ^{131}I-labeled serum albumin in the hypertonic saline and demonstrated increases in amniotic fluid volume of 50 ml within 2½ hours, 115 ml in 5½ hours, and 145 ml by eight hours after injection. The injection-to-abortion interval can be doubled, from 36 hours to 77 hours, by the administration of progesterone prior to injection of hypertonic saline.[7]

Wiest and his group,[18] as well as Short and co-workers,[19] have shown a 33 to 45% decrease in the concentration of progesterone in the peripheral plasma after intra-amniotic injection of hypertonic saline. (This work could not be confirmed by Kerr and his group[14] who were using 50% glucose as the hypertonic solution.) The shorter injection-to-abortion interval for patients with fetal death in utero or missed abortion, in comparison to patients undergoing elective middle-trimester abortion, indicates the significance of the normal progesterone potential of the placenta. Finally, correlation of the pathologic changes in the placenta with the clinical results obtained tends to verify the hypothesis that the hypertonic saline causes progesterone withdrawal.

Pathology

Strauss[20] studied the effects of hypertonic saline on the placenta, decidua, and fetal membranes of eight middle-trimester-abortion patients. Gross examination of the placenta revealed subchorionic zones of severe intervillous stasis over the entire surface of the placenta. On microscopic examination, the amnion appeared to be destroyed by an autolytic process. The chorionic villi showed variable damage with intervillous stasis, fresh thromboses, and large numbers of polymorphonuclear leukocytes. The trophoblast was frequently destroyed completely. The deeper portions of the placenta appeared normal, and the decidua showed occasional areas of necrosis and hemorrhage.

Electron microscopy has corroborated these pathologic changes. Thus, there is a necrotizing placentitis produced in the layers directly beneath the fetal surface of the placenta. The deeper layers, near the maternal surface, appear to remain normal, and no consistent lesions could be demonstrated in the fetuses examined. It is assumed that these severe structural changes in the placenta alter the production, transport, and concentration of progesterone, resulting in a progesterone-withdrawal effect which in turn causes evolution of uterine activity.

Clinical Aspects

From a clinical standpoint, one must weigh the inherent risks against the advantages to be gained from the use of this method to induce labor.

The Major Risks

The major risks involved include the possible introduction of infection into the amniotic cavity, the possibility of a direct intravascular injection of the saline, the possibility of fetal erythrocytes entering the maternal circulation due to damage of the placental vessels, and the possibility of injury to the bowel or bladder.

The Advantages

The advantages, on the other hand, seem to be numerous. The procedure is relatively simple to perform and is associated with a high success rate and a low incidence or morbidity. The induced labor is rather painless, and the injection-to-abortion interval is relatively short. In cases of therapeutic abortion beyond 12 weeks' gestation, the need for hysterotomy is obviated along with any risk to future childbearing, due to a scarred uterus. In cases of missed abortion or fetal death in utero, this method is useful in that with early induction of labor the risk of potential hypofibrinogenemia and the inevitable psychic trauma can be minimized.

Summary

The use of intra-amniotic injection of hypertonic solutions for the induction of labor appears to be uniformly effective and rapid and presents a minimum of disadvantages. It would seem to be an ideal method for the management of middle-trimester therapeutic abortion, fetal death in utero, or missed abortion. However, its use should be restricted to obstetrical units, and it should be performed only by personnel familiar with the technique.

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15-20. May be secured from the author or the reprints.

Imagination

One quality in which adult humanity is most deficient is imagination. All children have it; most adults have retained only scanty remnants. Perhaps our materialistic culture regards imagination as unmanly or morbid; or maybe imagination can germinate and flourish only in a fresh renaissance culture—which ours isn't. I often wonder whether practical scientists and technicians don't consciously stifle their remnants of imagination or unconsciously permit them to wither away. For instance, if I say that the top of my head feels as if it's floating or that the inside of my neck feels lumpy, my meaning is doubtless incomprehensible because of the listener's failure of imagination. (When I specify the inside of my neck, I mean the area between my throat and the outside of my neck.) Maybe my terseness is too surprising and hence disconcerting; perhaps it would be less confounding for me just to say: "I have a 'funny feeling' in my head or in my neck."—E.

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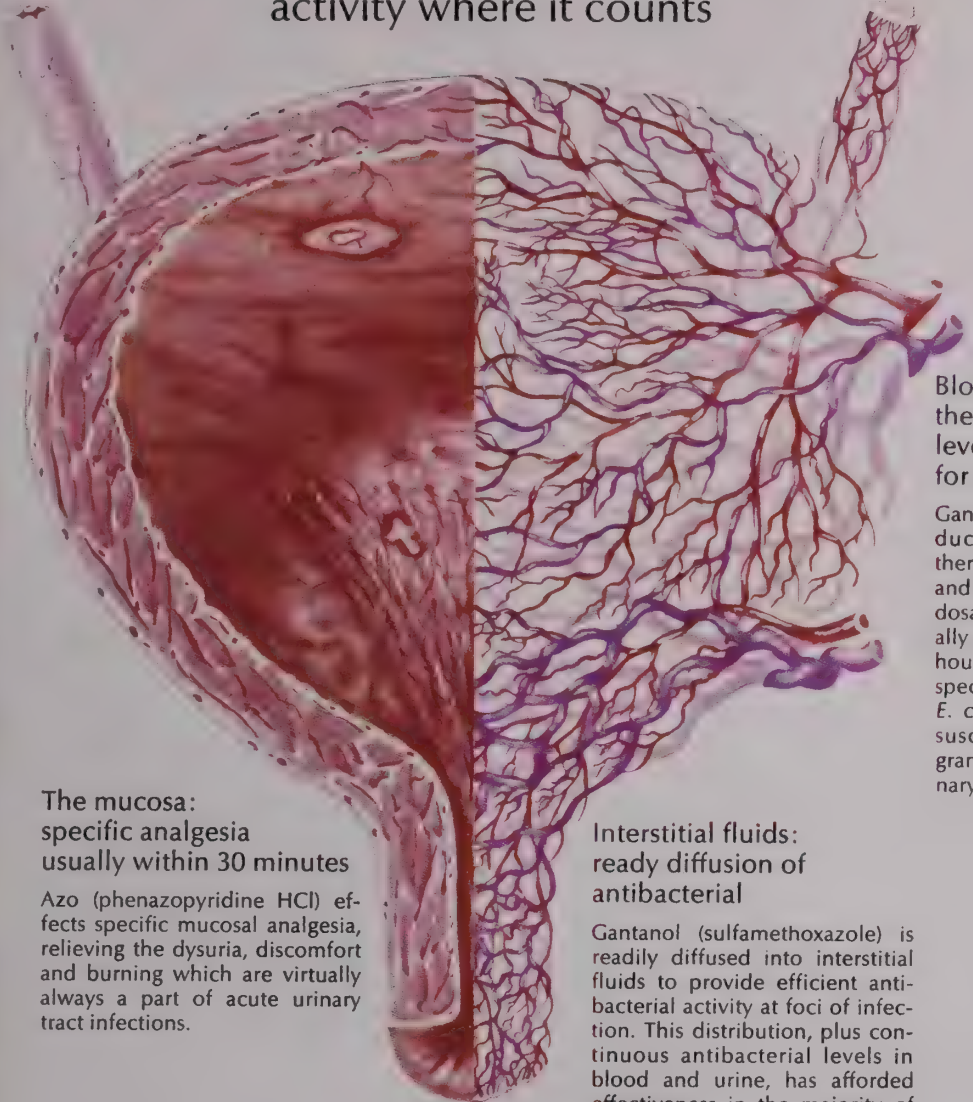

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Contraindicated in sulfonamide-sensitive patients, pregnant females at term, premature infants, newborn infants during the first three months of life, glomerular nephritis, severe hepatitis, uremia and pyelonephritis of pregnancy with gastrointestinal disturbances.

Warnings: Use only after critical appraisal in patients with liver damage, renal damage, urinary obstruction or blood dyscrasias. If toxic or hypersensitivity reactions or blood dyscrasias occur, discontinue therapy. In intermittent or prolonged therapy, blood counts and liver and kidney function tests should be performed.

Precautions: Observe usual sulfonamide therapy precautions including maintenance of an adequate fluid intake. Use with caution in patients with histories of allergies and/or asthma. Patients with impaired renal function should be followed closely since renal impairment may cause excessive drug accumulation. Occasional failures may occur due to resistant microorganisms. Not effective in virus and rickettsial infections.

Adverse Reactions: Headache, nausea, vomiting, urticaria, diarrhea, hepatitis, pancreatitis, blood dyscrasias, neuropathy, drug fever, skin rash, Stevens-Johnson syndrome, injection of the conjunctiva and sclera, petechiae, purpura, hematuria or crystalluria may occur, in which case the dosage should be decreased or the drug withdrawn.

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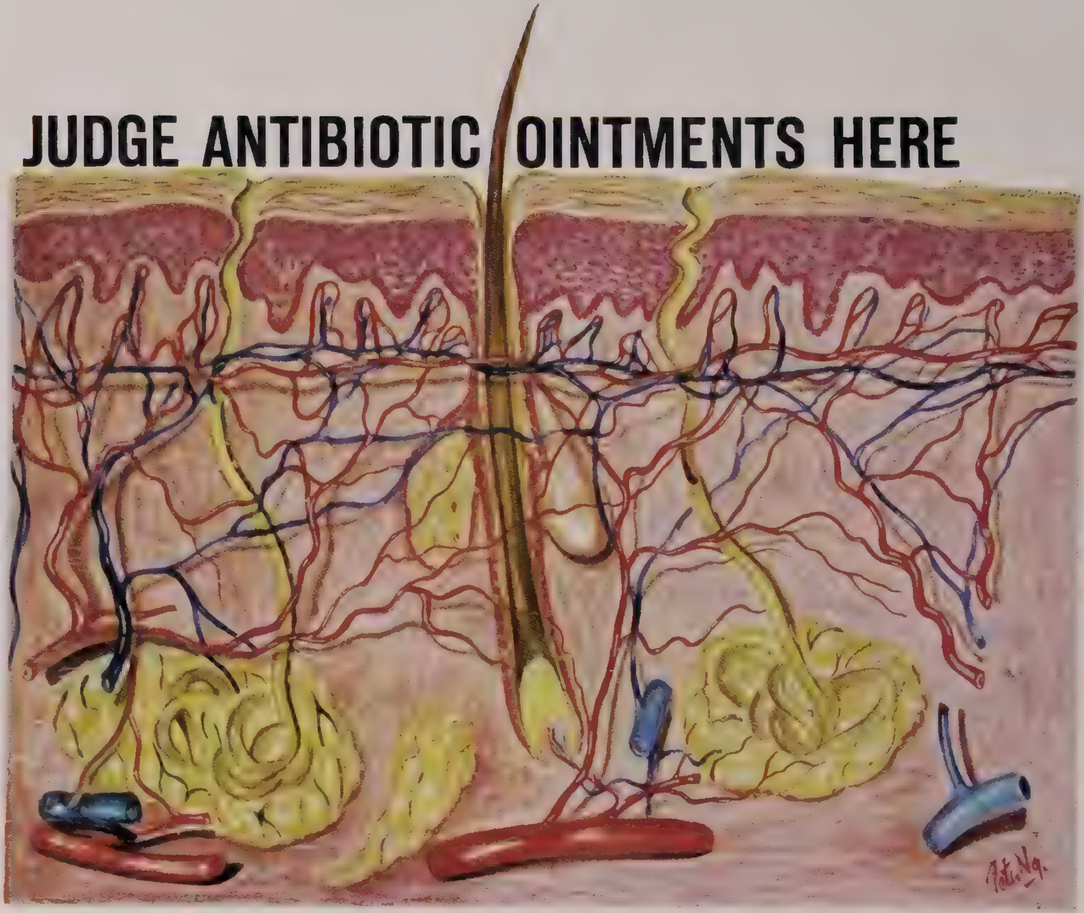

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Fracture Conference

More Problem Fractures in Children*

Dr. Anthony J. Bianco Jr.:†
Four challenging cases of children's fractures will be presented.

Case 1

Dr. John R. Sebald:‡
This 13-year-old boy was wrestling with his coach in a physical education class as a demonstration when he felt a "snap" in the upper part of his left arm. He came to the emergency room complaining of pain and discomfort on any movement of his arm (Figure 1-A).

Dr. Bianco:
Dr. Santos, what is the mechanism of forces that would produce this kind of injury?

Dr. Ray E. Santos:‡
I think that it is a twist or torsion type of injury.

Dr. Bianco:
It is typical of a torsion fracture—a spiral oblique type of fracture. The alignment of the fracture is reasonably good and there is no vascular injury.

Dr. Santos:
I think a hanging arm cast would do. You might attempt a little more reduction, probably by lowering the position of the arm, which would pull the distal fragment anteriorly.

Dr. Bianco:
If you are going to use a hanging cast, why would you try to reduce it first?

Dr. Santos:
You would not do any actual manipulation, but just try to return the arm to a normal position, and then apply the hanging cast.

---

*Fracture Conference, held at Mayo Clinic, March 25, 1968.

†Assistant Professor of Orthopedic Surgery (University of Minnesota), Rochester, Minnesota. Consultant, Section of Orthopedic Surgery, Mayo Clinic, Rochester, Minnesota.

‡Resident in Orthopedic Surgery, Mayo Graduate School of Medicine (University of Minnesota), Rochester, Minnesota.

Dr. Bianco:

With most boys of this age, it is hard to get them to comprehend the idea of sitting up with a hanging cast and letting it "hang." I think that this patient's mother sometimes put pillows under the boy's elbow because he was uncomfortable. He had a big swollen arm, and in addition his elbow was not really flexed enough. It is hard to get good control of the fracture with the hanging cast at 90° because if the hand drops, there is angulation. You must get the elbow flexed at more than 90°, I think, to get good control of the fragments.

Dr. Sebald:

This was the follow-up film that was taken at six weeks (Figure 1-B). He had been doing well: essentially everything that he did before—like playing the piano. Clinically, the union was solid. We let him wear the collar and cuff for two more weeks, and then these films were taken (Figure 1-C and D).

Dr. Bianco:

There is no angulation, is there?

Dr. Nikolaus D. Langloh:*

No.

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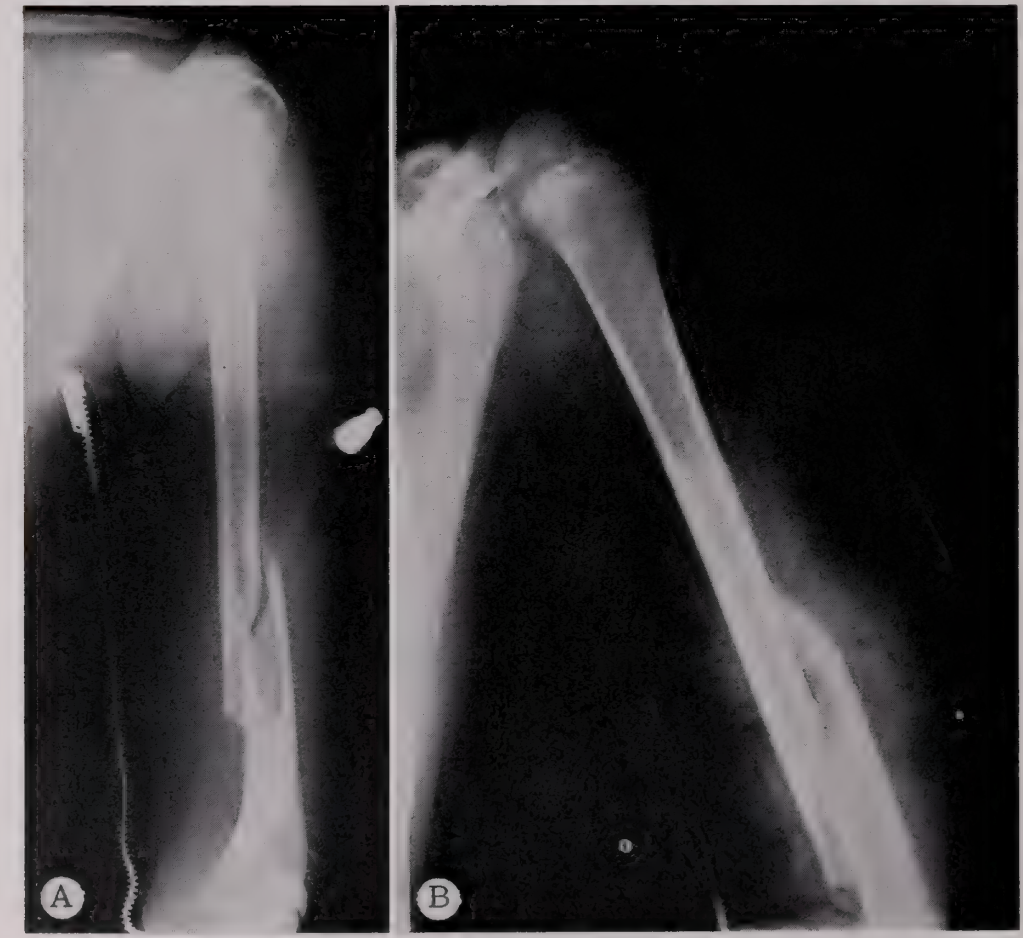

Fig. 1—(Case 1). (A) Spiral fracture of left humerus at junction of mid and distal thirds. (B) Six weeks after fracture, left humerus is in hanging cast.

Dr. Bianco:

Let us look at the films again (Figures 1-C and D). Here is a boy 13 years old. He has some shortening—1 cm or maybe more. His alignment, as you say, is good. I do not think there is angulation in any plane. We checked this carefully. Can we accept that?

Dr. Langloh:

Yes, if there is any shortening it probably will not be noticeable after the first few months.

Dr. Bianco:

First of all, the fracture occurred in the upper extremity. If some minor degree of shortening does result, it will be easy to disguise it. In a boy of this age, normal growth will even up the bones. If this were the femur or tibia of a 13-year-old boy, would you accept this reasoning?

Dr. Langloh:

Yes, I think the fracture itself will stimulate the growth rate so that there will be compensation for any loss of length.

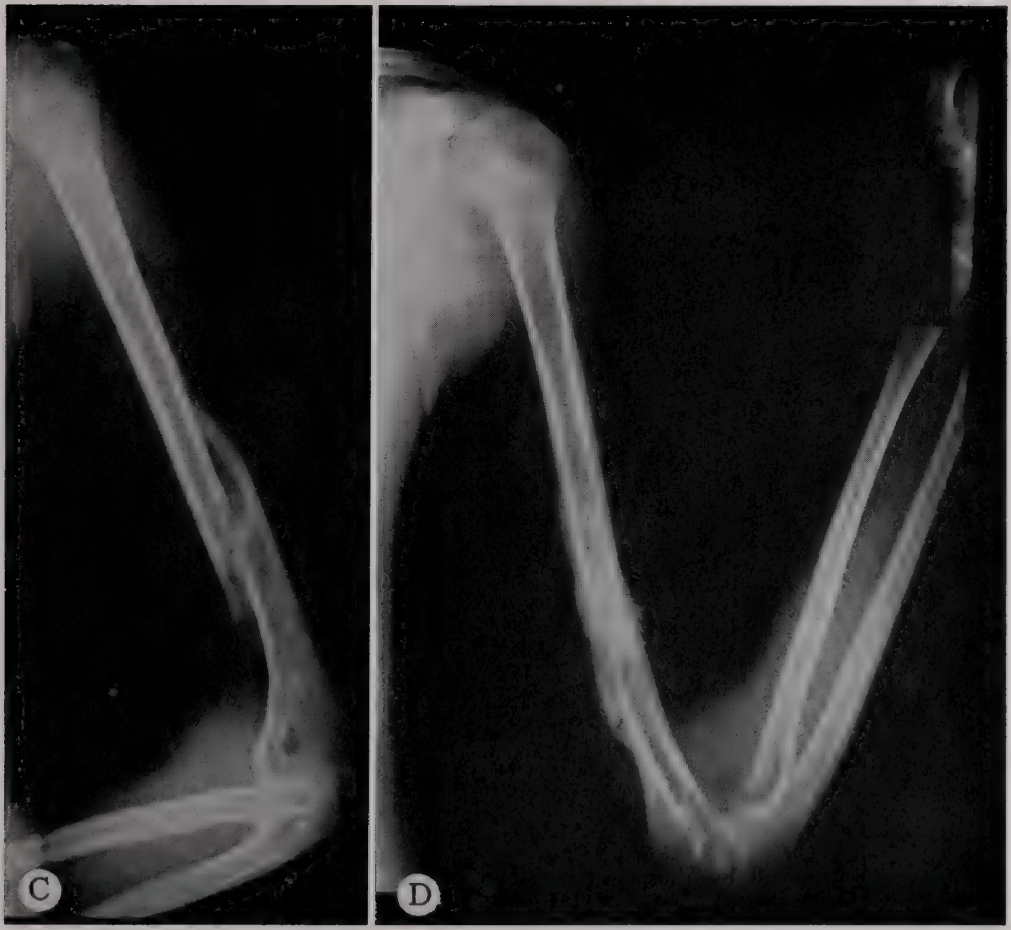

Fig. 1—(Case 1) (C) and (D) Anteroposterior and lateral views two months after fracture. Solid union, with no clinical deformity.

Dr. Bianco:

I agree. I accept this, too. In fact, this is desirable. I think that many have said that if you get an end-to-end reduction in a child this age, you are likely to get overgrowth temporarily. Dr. Johnson, were you going to say something?

Dr. Einer W. Johnson, Jr.:*

I agree with accepting a certain amount of shortening because there is always an increase in growth in a child after fracture of a long bone.

Dr. Richard S. Bryan:†

Just one comment about technique. You can, if you have a patient who is difficult like this one, set up a hanging arm cast, put a hook on the corner of the elbow, hang a three-pound weight off the foot of the bed, and you will get traction on the humerus, even if the mother puts pillows under the elbow.

Dr. Bianco:

This is a good point. The first week that he was in bed he had a tremendous amount of swelling and ecchymosis. During that period, I was not too con-concerned about it because I knew that as soon as he felt well enough, he would want to get up and get going, and he did. Once he got up, the arm did not have good position for the first week or 10 days, but it did not take long before the cast started to "hang." We changed the cast and flexed the elbow a little more and got what we wanted. Now, Dr. Lilly, you asked me something about a radial nerve injury at this time. What would you do?

Dr. Alan D. Lilly:‡

This is why I asked you. I have not made up my mind yet.

Dr. Bianco:

In a boy this age, I would wait and assess the effects of time.

Dr. Lilly:

If you have a radial nerve injury at this time what should be done? I have heard that nerve exploration is recommended.

Dr. Bianco:

I would not do an exploration in a boy of this age at this early stage. I think that most patients will recover if you wait. Now suppose, however, that six or eight weeks have passed and there is no sign of any return of radial nerve function, then I think there may be an argument for examining the nerve. But initially, no. Dr. Peterson, do you agree?

Dr. Hamlet A. Peterson:#

Yes.

Dr. Johnson:

I agree. One other important point concerns the proper splinting of the hand. I would use a dynamic splint or, if a dynamic splint was not available, I would put the wrist, fingers and thumb in hyperextension if there were a radial nerve injury. This is only good common orthopedic judgment, but for completeness we ought to mention that if there is a radial nerve lesion at this stage of injury, you can incorporate the hand splint in a hanging cast. While you are waiting for return of the nerve, the muscles supplied by that nerve should be protected by a proper splint.

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#Instructor in Orthopedic Surgery, Mayo Graduate School of Medicine (University of Minnesota), Rochester, Minnesota, and Consultant, Section of Orthopedic Surgery, Mayo Clinic, Rochester, Minnesota.

Dr. Bryan:

I have seen a patient who had the nerve caught at the fracture site and kept getting "electric shocks" distal to the site. This probably is reason for exploration of the nerve without delay.

Dr. Bianco:

The trend in treating patients who have radial nerve injuries and fracture of the humerus or humeral shaft is toward early exposure of the nerve. I am not saying you should just wait and wait indefinitely, but I think that in a child with this sort of fracture, particularly, you should not explore the nerve as your primary treatment but wait six to eight weeks. If there is absolutely no sign of any return of nerve function in six or eight weeks, then you are certainly justified in exploration. But most function returns by itself, I think. Any more questions about this case?

Dr. John H. Shertzer:*

If you explored the left arm now for a nerve lesion, what would you do with the fracture?

Dr. Bianco:

In this instance, if you have a complete radial nerve lesion, you must have stability of the bone on completion of the nerve repair, and I would use either a compression plate or some form of internal fixation—intramedullary nail or something—but probably a compression plate.

Dr. Allen P. Schlein:*

There was an article in the *Journal of Bone and Joint Surgery*† describing 45 of these radial nerve injuries and pointing out that manipulation of these fractures in an adult can damage the nerve.

Dr. Bianco:

If the radial nerve was normal before manipulation but was caught during manipulation, and this could be proved, I think the nerve ought to be explored immediately.

Dr. Johnson:

Another point about a hanging cast concerns obtaining good films. Often the roentgenologist will move the patient's arm away from his body in order to get a good lateral or anteroposterior view. I think a transthoracic, lateral, standing position is a good position in order to get a lateral view of the fracture without disturbing it.

Case 2

Dr. Sebald:

This 12-year-old boy, on December 23, 1967, fell backwards while ice skating, landing on his right arm (Figures 2-A and B).

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†Joseph L. Shaw—J Bone & Joint Surgery 494:899 July, 1967.

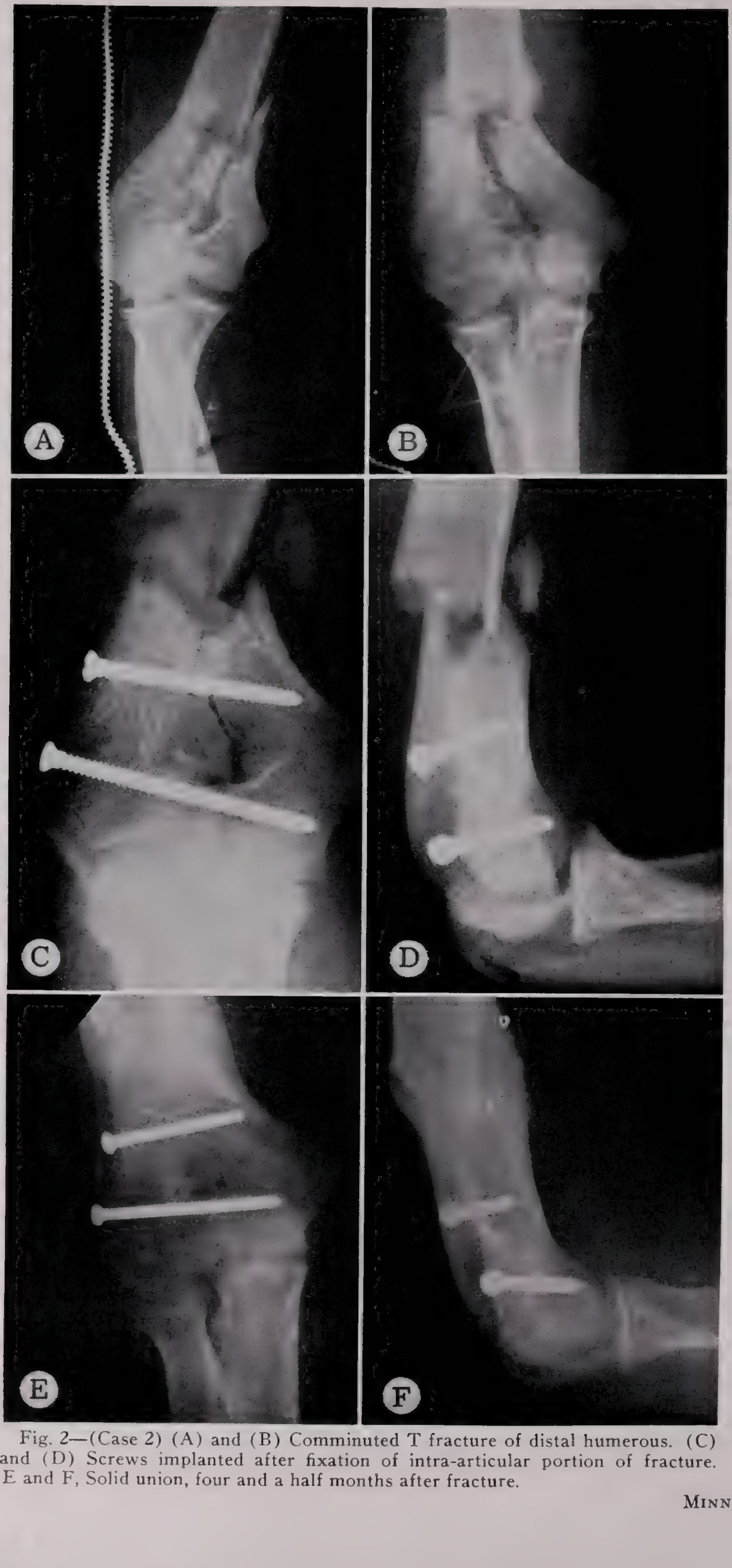

Fig. 2—(Case 2) (A) and (B) Comminuted T fracture of distal humerous. (C) and (D) Screws implanted after fixation of intra-articular portion of fracture. E and F, Solid union, four and a half months after fracture.

Dr. Bianco:

Dr. Chiroff, in a 12-year-old with much swelling but no evidence of vascular or nerve damage, what would you do?

Dr. Richard T. Chiroff:*

I assume that the fracture is not a compound one but a supracondylar fracture with extension to the area between the condyles. It also looks as if there is some rotation of the medial fragment.

Dr. Bianco:

There is an intra-articular component with some displacement.

Dr. Chiroff:

The radial head does not appear to be dislocated. I think closed reduction under general anesthesia would get some compression and molding of these fragments. Then I would put the boy in traction.

Dr. Bianco:

We have been told a lot about how children's bones grow and adapt and remodel, but what do you think about this? If we could get a reasonably good reduction, should we leave it alone and let it take care of itself?

Dr. Chiroff: I doubt whether this would develop into a perfectly normal arm if left as it is.

Dr. Bianco:

The fracture is down into the joint, between two articular areas of the elbow. Maybe we would not need to do anything about it.

Dr. William H. Bickel:†

I do not think the solution is as simple as it might be. There is external rotation of the medial fragment, and every time an articular surface is involved, you need a perfect reduction, if possible.

Dr. Bianco:

That is the point I am trying to make. This is an intra-articular fracture, even though it is between two major joint surfaces, and there is displacement.

Dr. Sebald:

The patient was placed in olecranon skeletal traction, but about four or five days later there was no improvement.

Dr. Bianco:

Why was this fracture not helped by longitudinal traction, Dr. Van Ness?

Dr. Noel T. Van Ness:* Because there was no lateral compression.

Dr. Bianco:

That is right. In other words, the force of displacement is lateral. We put him in traction, more or less, to control the swelling.

Dr. Sebald:

After surgery, a Robert Jones dressing was applied, and approximately one week later the patient was placed in a hanging cast.

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Dr. Bianco:

We have the intra-articular part of this fracture reduced under direct vision and have achieved good position (Figures 2-C and D). Now what about that transverse supracondylar fracture, Dr. Van Ness? Should we have done something about that? Should we put in a compression plate or use a "Y" plate?

Dr. Van Ness:

I do not think either would be necessary. You want to get better alignment of the joint even in a growing child.

Dr. Bianco:

Supposing this were a fracture in the same region but without the intra-articular involvement?

Dr. Van Ness:

You could put a pin through the olecranon. You would get fairly good alignment with this method.

Dr. Bianco:

I think this would be acceptable. Do you think you could handle it with a hanging cast?

Dr. Van Ness: No.

Dr. Bianco:

We put him in a hanging cast. We got the fracture reduced in surgery.

Dr. Sebald:

He was in the hanging cast for five weeks, during which time he had a severe rash under the cast and down the abdominal wall where the cast was rubbing; so we had to remove the cast.

Dr. Bianco:

Six weeks after the fracture, the cast was removed. These films were taken four and a half months after fracture (Figures 2-E and F). Clinically the result was good and the union solid. These films were taken with the arm in flexion because the boy could not extend his elbow. This makes it look as if he has a cubitus varus, which he did not have. His humerus is perfectly straight.

Dr. H. Peterson: When should the screws be removed?

Dr. Bianco:

I would not remove them unless the screw heads cause pressure or irritation. I would leave them where they are.

Dr. Bickel: I agree.

Case 3

Dr. Sebald:

Next is a 13-year-old girl who was turning cartwheels at home and fell on her left elbow, suffering what was probably a valgus strain. She came in with a sore, mildly swollen left elbow. These films were some of several taken in the emergency room (Figures 3-A and B).

Dr. Bianco:
Dr. Fuller, the girl fell while turning cartwheels, had a pain in her elbow, with limited motion. What is wrong?

Dr. Edwin B. Fuller:* The olecranon is dislocated.

Dr. Bianco: Correct!

Dr. Fuller: The left forearm seems to be a bit rotated.

Dr. Bianco: What about the tip of the olecranon in relation to the humerus?

Dr. Fuller:
It is a little lower on the left side, and it could be dislocated. I cannot tell definitely.

Dr. Bianco:
True, but something else is wrong with the way the joint surfaces fit. The olecranon is more distal than it should be. Look at the joint space where that peculiar object is. Compared to the normal other side, the joint surfaces are

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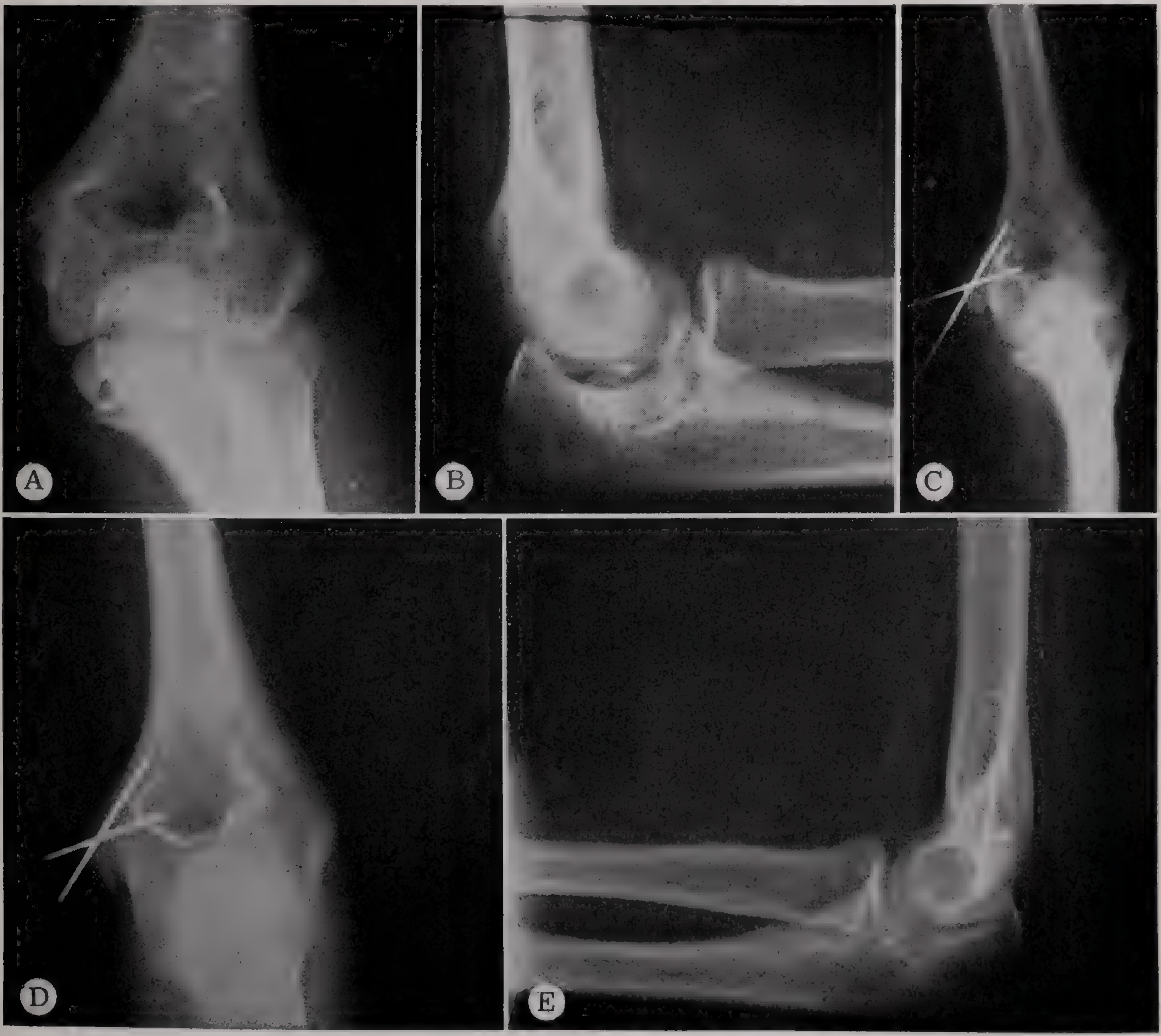

Fig. 3—(Case 3). (A) and (B) Avulsion fracture of medial epicondyle, with entrapment in elbow joint. (C) Operative film, K-wire fixation of medial epicondyle. (D) and (E) Anteroposterior view five weeks after fracture, just prior to removal of Kirschner wires.

parallel in the right elbow; they fit together very well. You say that elbow might be dislocated? What could be dislocated and still look like that? Let us assume, however, that it is dislocated.

Dr. Fuller: It could come from the tip of the olecranon.

Dr. Bianco: What could come from the tip of it?

Dr. Fuller: The fragment in the joint.

Dr. Bianco:
All right, the elbow is dislocated and there is a fragment in the joint. Look at the shape of the distal humerus, as compared to the other side. Look at the whole distal humerus. Something is missing. We have a fracture-dislocation with a fragment in the joint. The question is, where does this fragment come from and how big a piece do you think it is?

Dr. Rogers C. Southall:*
The medial epicondyle. We cannot see how big it is, but it is probably somewhat bigger than shown because of the cartilaginous condyle. It is not unusual for a medial epicondylar fragment to be displaced into the joint.

Dr. Bianco:
Right! My point is that the fragment is usually considerably bigger than this. This type of fracture is sometimes described as a condylar fracture, not an epicondylar fracture. More of the condyle is fractured off. What significance does this fragment have, other than being in the joint? Can you just take the fragment out?

Dr. Southall:
You have to leave the fragment intact. It represents growth of the medial epicondyle.

Dr. Bianco:
I imagine that you could get along without a medial epicondyle if you had to. What is attached to the fragment?

Dr. Southall: The flexors.

Dr. Bianco: The common flexor origin, primarily.

Dr. Sebald:
Because she had eaten recently, we placed her in a Robert Jones dressing with a plaster splint. She was taken to surgery the next day. The joint was approached medially, and it was immediately apparent that this fragment was, as Dr. Southall mentioned, a bit bigger than was apparent on the x-ray, but the common flexor organ was there and attached.

Dr. Bianco:
This was easier to do than I had anticipated. I expected a much bigger fragment. The whole medial side of the joint was obscured by a mass of muscle going into the joint, and once we retracted this common flexor origin out of the way, everything easily fell into place. Fortunately, we found the region where the epicondyle had fractured off, and it fit back very nicely (Figures 3-B and C).

Dr. Sebald:
A Robert Jones dressing was applied for one week, and she was placed in a long-arm cast.

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Dr. Paul R. Lipscomb:* Did you isolate the ulnar nerve? Did you see it?

Dr. Bianco:

No, the fracture was well anterior to it. We looked for it, but it did not seem that we were that much in the groove. The fracture seems to be more anterior.

Dr. Lipscomb:

Always look for the ulnar nerve.

Dr. Bickel:

If the fragment is small, do not try to use a screw.

Dr. Bryan:

If you see such a fragment early, you can often get the fragment from the joint by having the patient tense his flexor muscles.

Dr. Bianco:

That is a good point. I have never tried it. What impressed me was that after we got the fragment from the joint, there were no medial ligaments stabilizing the elbow. Everything on the medial side was ruptured, and even with the fragment out of the joint, you could spring the elbow wide open. There were no other structures stabilizing the medial side of the joint. This is another reason for getting a good anatomic reduction. There is no medical stability of the elbow.

Dr. Bickel:

I do not think you have to worry about the ulnar nerve in a small fracture like this, but the ligaments and the muscles must be repaired. You lose stability if you do not put the condyle back.

Dr. Sebald:

This is the final x-ray just prior to removal of the K wires (Figures 3-D and E).

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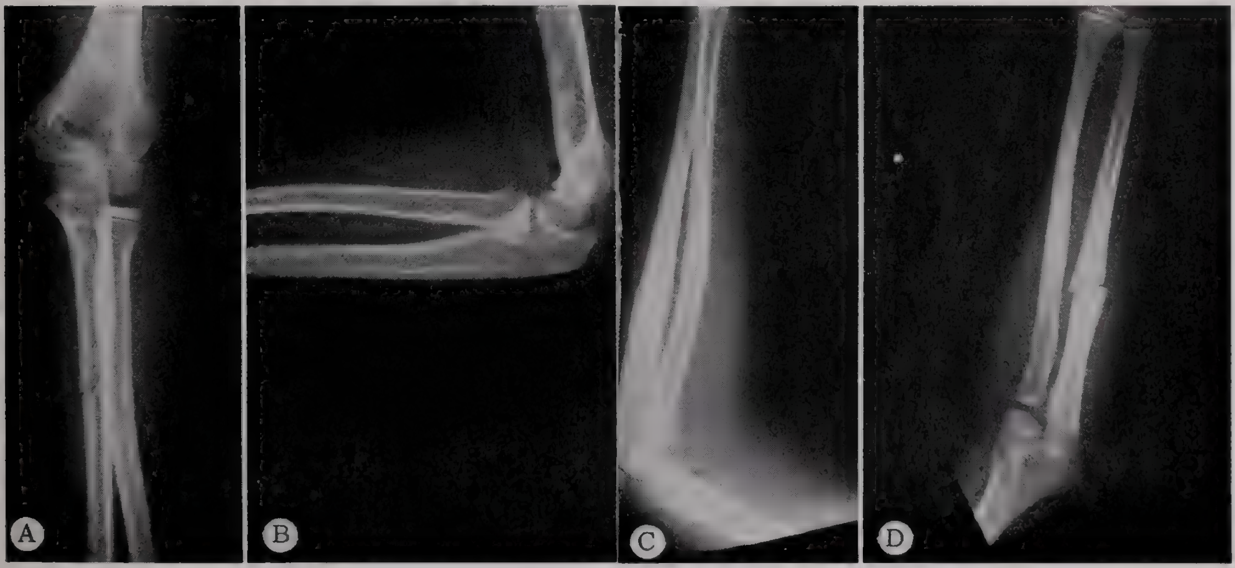

Fig. 4—(Case 4). (A) and (B) Undisplaced fracture of left ulna. (C) and (D) Refracture of left proximal mid ulna 10 weeks after initial fracture.

Case 4

Dr. Sebald:

The next case is of a seven-year-old girl who fell off a swing and landed on her left arm. When she came to the emergency room, she had pain and swelling just distal to the left elbow (Figures 4-A and B).

Dr. Bianco:

Dr. Turner, do you see anything there?

Dr. Richard H. Turner:*

There is an undisplaced disruption of the ulna.

Dr. Bianco:

Do you think we ought to break through the other side of the cortex?

Dr. Turner:

This should be considered because it appears that the fracture is a greenstick fracture of the ulna even though it is without disruption of the cortex. When you have a fracture through one side of the cortex in a child, the other side of the cortex should be broken lest discrepancy in the length and bowing develop in healing.

Dr. Bianco:

I am not entirely convinced there is a fracture of the radius. This may or may not be visible on the initial films (Figure 4 A and B). The fracture is undisplaced. Dr. Peterson, would you consider this?

Dr. H. Peterson: Just immobilize it.

Dr. Bianco:

That is just what I did. The other side of the cortex should be broken when

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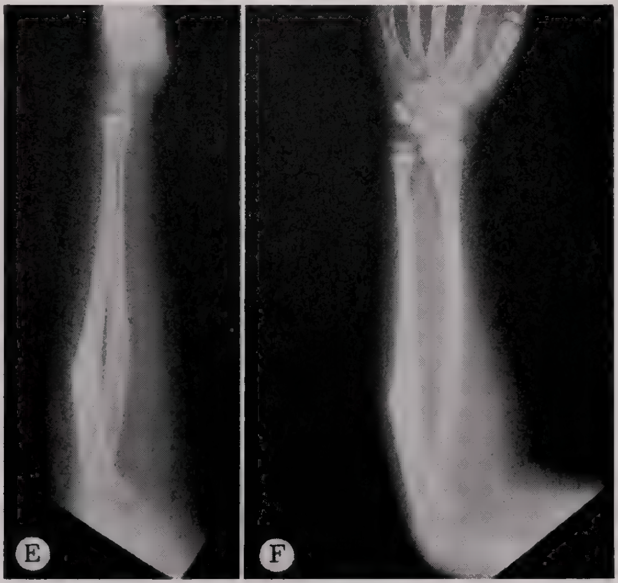

Fig. 4—(Case 4) (E) and (F) Anteroposterior and lateral views 11 weeks after refracture.

you have a greenstick fracture of both bones near the wrist and also have angulation, but this is really an undisplaced fracture.

Dr. Sebald: She was put in a long-arm cast.

Dr. Bianco: Now the question is how long should you hold this fracture?

Dr. Turner: I think that in a child I would hold it about five weeks.

Dr. Bianco: How long did we hold it?

Dr. Sebald: Four weeks.

Dr. Lowell F. A. Peterson:*
One thing was mentioned that I would like to have explained. Dr. Turner, you were worried about crooked overgrowth in the ulna. Is that what you meant to say?

Dr. Turner:
It is my impression that, when you have a fracture through one side of the cortex, the callus formation will hypertrophy that side of the bone and produce a convexity to the side where the fracture was.

Dr. L. Peterson:
You think that the bone increases in length at that side over what it was at the time of the fracture?

Dr. Turner: Yes, that is my impression.

Dr. L. Peterson:
I do not think that happens. Overgrowth is longitudinal at the epiphyseal end, and the angulation you have is not due to an overgrowth.

Dr. Bianco:
The concern with greenstick fractures is primarily the recurrence of the angulation, and I think you have to have some angulation to start with. Do you believe in completing a greenstick fracture for its angulation?

Dr. Bickel:
Most times, yes.

Dr. Bianco:
Considering Volkmann's contracture of the forearm in general, can anyone tell us how many resulted from supracondylar fractures of the humerus and how many resulted from fractures in the forearm?

Dr. Lipscomb:
In the cases we studied a few years ago, about 80% of the fractures were from injury around the elbow rather than in the forearm.

Dr. Bianco:
Here is an undisplaced fracture. So far, everyone agrees that we should put this child in a long-arm cast to hold the fracture.

Dr. Joe L. Nettles:†
Was there any evidence of dislocation of the head of the radius?

Dr. Bianco: No.

Dr. Shertzer:
Did you have an x-ray of the wrist on the initial examination?

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Dr. Sebald:

Yes. She was immobilized four weeks, and then the cast was removed, and she was told to be careful for two weeks. She was seen at that time and was clinically normal, had good motion, no pain, and no discomfort.

Dr. Bianco: Now six weeks have passed without any trouble.

Dr. Sebald:

Ten weeks after the original injury, she was playing at home and bumped her arm—apparently not too great a traumatic incident—and experienced much pain in the same region of the left forearm.

Dr. Bianco:

So all our arguments about completing the fracture were for nothing. She did it herself 10 weeks later (Figures 4-C and D). She had plenty of periosteal new-bone formation there. From everything I had to go on, this fracture was solidly united. Ten weeks after the injury, there was another incident of trauma. From the appearance of the periosteal new-bone formation, you would think this would have broken somewhere else. My only point in bringing this up is that this region of the ulna just does not heal as rapidly as we think. The trauma did not seem to be severe, and yet she suffered a refracture.

Dr. Sebald:

This time, she was put in a long-arm cast for about seven weeks.

Dr. Bianco:

There is much evidence of healing again. How long has it been now?

Dr. Sebald:

This is 11 weeks after the refracture (Figures 4-E and F).

Dr. Bianco: Is she doing all right now?

Dr. Sebald:

Yes, she was seen one more time one month ago. She had complete range of motion and no discomfort.

Dr. Johnson:

Generally, a fracture in the distal forearm with 15° or more of angulation should be manipulated. Is that right?

Dr. Bianco: And is the fracture completed?

Dr. Johnson:

I think that you cannot manipulate a fracture without completing it.

Dr. Bianco:

Sometimes you do not, unfortunately, complete the fracture. Sometimes you just bend the bones out straight again and put them in a cast and you get excellent position, but only one side of the cortex is fractured. And six weeks later, the angulation is right back where it was when the bone was fractured originally. I believe the greenstick fracture should be completed. The non-completed fractures are the ones that result in the bone springing back, even when there is a good cast. I do not see much reason to manipulate or complete a greenstick fracture that is undisplaced. If it is in anatomic position, I do not think you are accomplishing anything by completing the fracture. Fractures that are angulated, are angulated on one side, with the other side intact, and I think these have a tendency to become deformed again.

Conclusions

These cases have illustrated some points in fracture management:

1. Radial nerve lesions in children should be approached conservatively and explored only if the nerve is cut or caught between the bone ends. If function of the nerve does not occur within six to eight weeks, exploration is indicated.
2. Fractures that involve the joint surfaces should be reduced as accurately as possible to forestall degenerative joint changes in later life. And when a bone fragment is "locked" in the joint, surgical removal is mandatory.
3. Angulated greenstick fractures tend to return to their deformed position unless the "intact" cortex is fractured.

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The cover photograph was taken on the North Shore of Lake Itasca near the main camp grounds about 8:00 p.m. using Kodachrome II film, 1/60 sec. at f2.8. The camera was a Pentax—single lens reflex 35 mm.

Specialization Versus Coordination*

Though we may deprecate specialization for the problems it may introduce, its growth is essential to the continued practice of medicine. To the extent that it does flourish, there is concomitant need for integration, interpretation and generalization. The value systems, methods and organization of medical education and practice have adapted well to the needs of society for training of specialists but have left largely unsolved the corollary development of equal stature for the integrating function of medicine. We now face the task of interweaving the benefits of specialization into general medical care. Neither the internist nor the general practitioner as presently constituted are equipped to perform optimally this integrating function. A new kind of generalist is required, not just the introduction of general practice into medical education.†

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*See Editor's Soliloquy. Page 763.
†E. D. Pellegrino in Richard Magraw: Ferment in Medicine, 1966.

WHAT'S SO WEAK ABOUT THE WEAKER SEX?

IMPROPER PAGINATION IS
PUBLISHER'S ERROR

Clinical Path Conference

Acute Renal Failure
Hypernephroma in Middle-Aged Woman

Dr. Hugh Edmondson:*

A 60-year-old white female was admitted because of acute renal failure.

Three days before admission the patient had entered the hospital in a small Minnesota community complaining of weakness and diarrhea which had been present for about two weeks. She had been drinking water and boiled skimmed milk for several days before admission, with no improvement. Very little past history was obtained at that time, but she had apparently been in satisfactory health previously. There were no known inherited diseases in her family.

At the time of this initial hospitalization she had a temperature of 100.4°. Blood pressure was not recorded. She was described as dehydrated, fat, and able to speak coherently but weakly. Physical examination of the head, eyes, ears, nose and throat was normal. There were no palpable lymph nodes. The lungs were clear. The heart was of normal size with regular rhythm and normal heart sounds. No murmurs were heard. The abdomen was described as protuberant and obese and no organs were palpable. Pelvic and rectal examination was not performed. A trace of edema was observed in the lower extremities. Neurological examination was normal. Her hemoglobin was 10.9 gm %; white blood count 14,300 with 90% neutrophils. The urine had a specific gravity of 1.026, was negative for albumin, but gave a 3 + test for sugar. Large amounts of yeast were noted in the urine but no white or red blood cells. A chest roentgenogram reportedly revealed an area of consolidation in the right lower lobe.

The following morning her temperature was 102°; respirations were 60 per minute. She was cold, pale and clammy. A thoracentesis was attempted (apparently in the right hemithorax) and 5 cc of bloody fluid were removed. Her blood pressure fell and could be maintained only by intravenous administration of Metaraminol and hydrocortisone. The urine output remained adequate. At this time the blood glucose was 560 mg % (intravenous solutions containing glucose were being administered); serum sodium was 147 mEa/L; potassium 4.7 mEq/L; chloride 96 mEq/L and CO_2 combining power 36 vol % (normal 55 to 75 vol %). The blood urea nitrogen was 45 mg %; hemoglobin 8.6 gm %, white blood count 10,850. Intravenous insulin was administered and she was given transfusions of three units of whole blood.

On the third hospital day her hemoglobin was 12.5 gm %; her white blood count 13,350 with 85% neutrophils; her blood glucose 500 mg %. She was then transferred to a private hospital in Minneapolis. On admission she was hypotensive and required continuous infusions of vasopressive agents including norepinephrine and isoproterenol. Her blood urea nitrogen was 129 mg %; her blood glucose 398 mg %; her serum acetone negative. Serum sodium was 147 mEq/L; potassium 4.8 mEq/L; bicarbonate 27 mEq/L; chloride not recorded. The

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patient was observed to be oliguric and failed to attain adequate urine output after intravenous administration of 25 grams of mannitol and 50 mg of ethacrynic acid.

Six hours after this admission she was given 0.5 mg Lanoxin intravenously and 50 units of regular insulin subcutaneously, and was transferred to Hennepin County General Hospital.

Physical Examination

On admission the patient appeared to be moribund, was obese, unresponsive and edematous. Her pupils were small, equal and reacted poorly to light. Her mouth contained dried secretions. Respiratory excursions were shallow and symmetrical. Coarse rales were heard over the lower half of both lung fields and breath sounds were poorly audible. The cardiac impulse was barely palpable, but no murmur or gallop rhythm could be heard. The abdomen was described as obese with no palpable organs. Pelvic and rectal examinations were not performed. Extremities were pale and cyanotic. There was minimal response to painful stimuli, but no focal neurological defects were observed. Blood pressure was recorded as 40/0; temperature was 97.2°; pulse 110. The central venous pressure was 4.5 cm of water.

Hospital Course

An endotracheal tube was inserted and respirations were supported with a mechanical ventilator. Blood pressure was maintained with a continuous intravenous infusion of isoproterenol and Levophed. Five percent sodium bicarbonate was administered at a rate of 60 cc per hour. A chest roentgenogram was obtained.

On admission her hemoglobin was 13.4 gm %; white blood count 11,600 (no differential); serum sodium 149 mEq/L; potassium 5.5 mEq/L; chloride 100 mEq/L and bicarbonate 27 mEq/L. Blood glucose was 715 mg %. Fifty units of regular insulin were administered at the time of admission. During the 24 hours after admission the patient remained unresponsive. Her temperature rose to 102° and her urine output was only 20 cc. Twenty-four hours after admission her hemoglobin was 9.6 gm %; hematocrit 28%; platelets were felt to be adequate. Her serum sodium was 151 mEq/L; potassium 6.3 mEq/L; chloride 86 mEq/L and bicarbonate 21 mEq/L. Her prothrombin time was 63 seconds with a normal control; fibrinogen was 126 mg %. Her blood pressure became increasingly unstable and finally imperceptible. She expired. An autopsy was performed.

Clinical Discussion

This is an interesting patient who presented with a brief illness characterized primarily by diarrhea with rapid progression into a state of hypotension and shock. In reviewing the protocol, there are certain points that are important for our discussion. Apparently she had been in good health prior to the onset of this illness, with no evidence of chronic disease. Her family history was noncontributory. It is significant that her primary examination in the first hospital was remarkably normal except for dehydration and weakness. A low-grade fever and a trace of edema were noted. She had no evidence of disease in the gastrointestinal tract at this time. Important laboratory data include a significant leucocytosis with a left shift, glycosuria, anemia of 10.9 gm%, and a chest x-ray revealing an area of possible consolidation in the right lower lobe. It is also significant that her temperature rose to 102° the following morning.

At this time she developed clinical shock and remained in shock apparently for the remainder of her four days of life. Her initial blood sugar was elevated at 560 mg% and her CO_2 combining power was slightly decreased. After transfusion the hemoglobin rose to 12.5 gm% and she was transferred to another hospital in this area. At the time of transfer here she was still hypotensive; her blood urea nitrogen was 129 mg%, blood glucose 398 mg% and her serum acetone negative. Electrolytes at this time were within normal range. This is the first mention that we have of low urine output. Mannitol and ethacrynic acid failed to improve urine output. Because of the persistent oliguria, she was transferred to Hennepin County General Hospital for treatment of her renal failure.

At the time she arrived at this hospital she was moribund, dehydrated, unresponsive, and showed signs of respiratory distress. Quite significantly, the abdominal examination again was apparently unremarkable except for obesity. In spite of heroic measures at this hospital with supported respirations via a mechanical ventilator, continuous infusion with isoprel and Levophed and intravenous therapy, she expired within 24 hours. Significant laboratory data on this final admission revealed a relatively normal white count of 11,000, essentially normal electrolytes, and a markedly elevated blood glucose of 715 mg%. It was only terminally that the electrolytes were noted to be somewhat abnormal. At this time her serum sodium was 151 mEq/L and potassium 6.3 mEq/L. Two other laboratory values of significance terminally were a prothrombin time of 63 seconds and a fibrinogen of 126 mg%.

We might begin our discussion of the differential diagnosis by considering the pulmonary problem. I don't believe this was a major cause of her illness, but nevertheless she did present with a right lower lobe consolidation, rales, fever and respiratory distress. Could we see the x-rays now, please?

Dr. Oscar Lipschultz:*

The films that we have taken at this hospital are inadequate for interpretation. These are supine films. There is a haziness in the right lower lobe, and whether this represents a distinct consolidation or not is difficult to determine. We do not have the x-ray films from the other hospitals.

Dr. Edmondson:

Interpretation then of the x-rays are that they are not much help at all. Is that correct?

Dr. Lipschultz:

That is correct.

Dr. Edmondson:

With a patient who presents with pulmonary consolidation and bloody pleural fluid, we have to consider an infectious process and pulmonary emboli. However, I do not think we have enough evidence to establish a clear diagnosis in this area or to distinguish between these two possibilities. One must also consider a dissection of an aortic aneurysm in a patient who has such a rapid demise.

Let us now consider the gastrointestinal aspect of her disease. Her one complaint on admission was diarrhea. It is worthwhile at this time to review the etiology of this complaint. Diabetes needs to be strongly considered in this lady because she was elderly and obese and had a persistently elevated blood sugar. Diabetics certainly can have recurrent episodes of diarrhea. This presumably is due to the diabetic effects on the nerve supply to the gut. This usually is an intermittent type of diarrhea which rarely is severe enough to cause dehydration to this extent and certainly would be unlikely to produce a state of shock. It is not clear to me whether she did have diabetes; but I don't believe this was her underlying problem. The second possibility that needs to be strongly considered in such a rapid downhill course is a mesenteric vascular catastrophe. An elderly, obese, possibly diabetic lady would certainly be a good candidate for mesenteric vascular insufficiency. However, the fact that she had no evidence of vascular disease in other areas tends to rule against this possibility. These patients usually present with a history of abdominal pain, usually following meals, and weight loss. Frequently this condition will lead to an audible bruit in the upper abdomen.

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*Staff Radiologist, Hennepin County General Hospital.

Other causes of diarrhea would include the various inflammatory diseases of the small and large intestines. Elderly patients certainly can present with fulminant regional enteritis or ulcerative colitis. The fact that she did not have a bloody diarrhea would tend to rule out ulcerative colitis. The absence of a previous history of gastrointestinal complaints also would tend to exclude these disease entities. The possibility of bacterial or parasitic infections also exists. However, without stool studies or cultures, it would be pure guess work to implicate a specific etiologic agent. We also lack the benefit of a rectal examination or a barium enema.

The possibility of peptic ulcer with its complications should be considered, but against this is the lack of a previous history suggesting peptic disease. Also, after two weeks of diarrhea, she showed no evidence that she was hemorrhaging into the gastrointestinal tract. Therefore, I think a bleeding peptic ulcer would be unlikely. However, a perforated peptic ulcer can certainly be present in the older age group with rapid progression to peritonitis and shock, but the absence of abdominal tenderness or signs of a surgical abdomen would tend to rule against this diagnosis.

I believe the gallbladder area sounds more promising. An elderly, obese, possibly diabetic lady would be a prime candidate for gallstones. Complications of gallstones that need to be considered are an acute cholecystitis with perforation of the gallbladder or an acute ascending cholangitis with development of multiple hepatic abscesses. But the absence of a good history makes these diagnoses tenuous. Lack of an enlarging liver or a tender liver or jaundice tends to rule against ascending cholangitis with liver abscesses. The absence of abdominal pain, vomiting and tenderness in the upper abdomen would tend to rule against the diagnosis of pancreatitis; also, constipation would be more in keeping with pancreatitis rather than diarrhea. The absence of pain and abdominal tenderness, however, does not completely exclude pancreatitis. Painless pancreatitis may occur.

Perhaps a review of some of her other abnormal clinical findings will give us a clue to the underlying disease. She apparently was febrile on first examination and remained febrile throughout her course. This, of course, would be perfectly consistent with a lobar pneumonia. However, it would also be consistent with any inflammatory disease below the diaphragm. She also was anemic throughout her course, a fact which remained a main stumbling block in establishing a diagnosis. The initial hemoglobin was 10.9 gm%, but this probably was not an accurate estimate of her blood volume because of her initial dehydration. The hemoglobin of 8.6 gm% after administration of intravenous fluids is probably a more accurate value. The fact that she dropped from a hemoglobin of 13.4 gm% to a hemoblogin of 9.6 gm% in less than 24 hours after arrival at this hospital would certainly suggest the possibility that she was hemorrhaging, most likely in the abdomen. I do not believe there is enough evidence on x-ray to suggest that she had a massive hemorrhage into the thoracic cavity to explain the blood loss. The lack of documentation of gastrointestinal bleeding is disturbing. The stools are not described. This might suggest that the blood was lost in an area that was not directly communicating with the gastrointestinal tract. The persistent azotemia, I believe, is just a manifestation of the persistent shock state. She arrived with a BUN of 45 mg%, and this rose to over 100 mg%. I believe this represents a prerenal azotemia. I do not believe we have to implicate acute or chronic renal disease.

Now, is it possible to tie all this information together and explain it on the basis of one disease? I believe the one which would best explain much of her course would be a disease of the pancreas. Patients that present with an acute hemorrhagic pancreatitis can have a speedy course with shock and rapid demise. I think the fact that she was weak and lethargic at the time of her initial presentation and had had symptoms for several weeks might explain the failure to obtain a history suggestive of pancreatitis, such as abdominal pain, nausea and vomiting. One might also have expected to be able to elicit some tenderness in her abdomen on initial examination; however, it is well known that abdominal examinations in elderly, obese individuals can often be misleading.

Hemorrhagic pancreatitis could readily explain the anemia. It is known that patients with hemorrhagic pancreatitis can have rapid loss of blood into the necrotic tissue. The persistently elevated blood sugars would easily be explained on this basis as well. Again, it depends on how much of the pancreas is involved; but it is known that many patients with acute pancreatitis initially have elevated blood sugars. I do not believe that she can be considered a straightforward diabetic because, in spite of these extremely elevated blood sugars, she showed no evidence of ketoacidosis. The changes noted in the blood clotting system in the terminal admission are also consistent with acute pancreatitis. For some reason, patients with acute pancreatitis may have alterations in their clotting factors, and the prolonged prothrombin time and the lowered fibrinogen level would be compatible with this.

I think for the sake of completion we should consider an acute vascular catastrophe involving the mesenteric vessels or the abdominal aorta. This condition would explain the shock-like state, the anemia, and her rapid deterioration. The possibilities of myocardial infarction and vascular abnormalities in other areas probably do not apply in this case.

In summary then, I think this elderly lady had acute hemorrhagic pancreatitis with rapid deterioration. She may have had gallbladder disease as the initial cause of the pancreatitis. Gallstones and stones of the common duct may well be found at autopsy. She may or may not have diabetes.

Dr. Andrew Edin:*

How often when you have a case of hemorrhagic pancreatitis do you see findings in the chest?

Dr. Edmondson:

This can occur. Pneumonia, atelectasis, and bloody pleural effusion have all been described. These, however, are usually present in the left chest, and this patient presented with right-sided findings.

Dr. Robert Strom:†

Would you comment on the amylase levels in renal failure and also on the hemoglobin concentration in acute interstitial pancreatitis vs. that in acute hemorrhagic pancreatitis.

Dr. Edmondson:

We do not have amylase studies available; perhaps they were not done.

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†Associate Pathologist, Hennepin County General Hospital.

I think when the patient arrived at this hospital in her moribund state, the damage to the pancreas may have been so severe that normal amylase levels might have been obtained. In acute interstitial pancreatitis there is usually an elevation of amylase values; but in the severe hemorrhagic pancreatitis one might not get elevations. In regard to the hemoglobin levels, I can only guess bleeding was probably the main manifestation of her problem. Perhaps if she had been seen a week earlier in her illness, evidence of hemoconcentration might have been present. It is a little hard to explain this extreme anemia and particularly the rapid drop in hemoglobin that was observed in the last day of her life by bleeding into the pancreatic area alone. Perhaps she did have some other complication in the abdominal area which led to bleeding.

Dr. Fred Shapiro:*

We see very rapid development of anemia in acute renal failure, and this factor may have been contributory to her anemia.

Dr. Edmondson:

Do you think a BUN of over 100 is adequate explanation for dropping her hemoglobin almost 4 gm% in 24 hours?

Dr. Shapiro:

I think in situations like this there is a marked hypersplenic effect leading to increased destruction along with the marrow suppression.

Dr. Edin:

Will you comment on the amylase levels in patients with renal failure who do not have pancreatitis?

Dr. Shapiro:

These levels can be extremely variable. In general, they tend to be normal. We never have seen any patients with amylase levels over 500 who are in acute renal failure. Sometimes they will be elevated to 300 or 400, however.

Dr. Strom:

It should be borne in mind that amylase levels in pancreatitis can be often elevated in abnormal collections of fluid, for example, in the pleural space and the pericardial cavity. Determining amylase levels on these fluids can often be of extreme diagnostic importance.

Dr. Edmondson:

This also can be applied to fluid obtained by needle aspiration of the peritoneal cavity as well.

Pathology Discussion

Dr. John Crosson:†

The external examination of the body revealed marked obesity and numerous ecchymoses over all extremities. This probably was a manifestation of the bleeding tendency to which Dr. Edmondson alluded. She also had pronounced xanthelasma of her upper eyelids. When the abdomen was opened, extensive fat necrosis involving all the peritoneal surfaces was seen, both in the upper abdomen and also in the pelvis. There was a small amount of dark fluid present in the abdominal cavity. In the upper abdominal cavity, there was extensive necrosis involving the entire region occupied by the pancreas. Numerous tiny green-grey stones measuring from 1 to 2 mm in diameter were found in the gallbladder. When the common bile duct was probed, many of these tiny stones were pushed through the Ampulla of Vater into the duodenum.

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Figure 1 shows a picture of the common duct opening into the duodenum. The grey tissue around the common duct represents the necrotic pancreas. The pancreatic duct opened directly into the common bile duct 4 mm proximal to the Ampulla of Vater. Therefore there was a common channel measuring 4 mm which drained both the pancreatic secretions and the bile. The pancreatic duct was traced into the pancreas and then suddenly was lost 6 cm from the Ampulla in the necrotic substance of the body and tail of the pancreas.

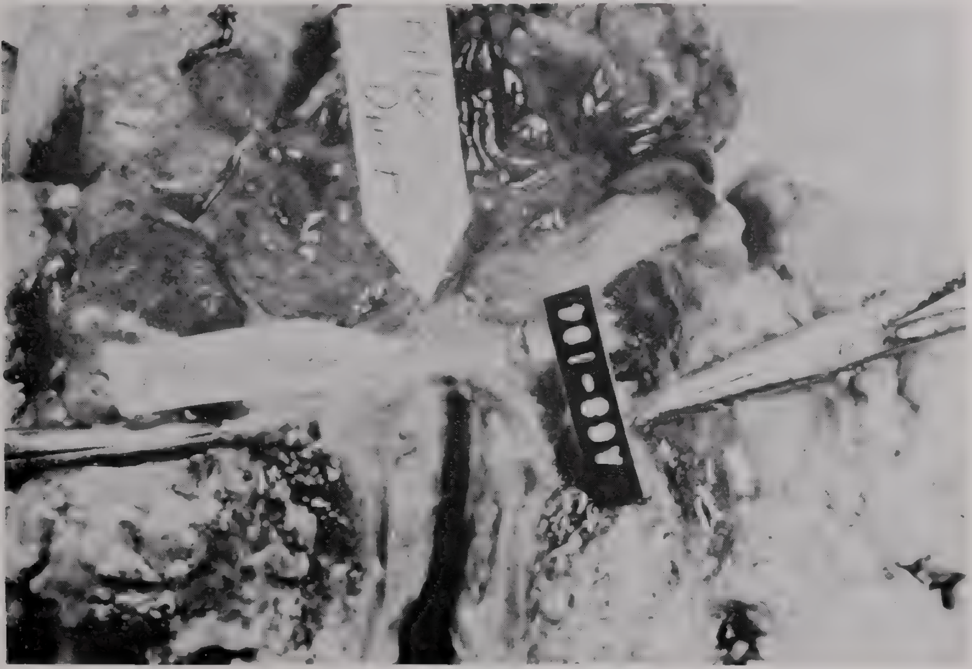

Fig. 1—Acute Pancreatitis

Figure 2 shows viable pancreatic tissue at one corner with marked acinar dilatation. There is also marked edema of the interstitial areas. The rest of the picture shows necrotic tissue and some hemorrhage. The necrotic tissue cannot be recognized as pancreas. There is a very sharp demarcation between the viable pancreatic tissue and the necrotic tissue. This very sharp demarcation, which is characteristic of pancreatitis, has suggested to some authors that much of the necrosis in pancreatitis might be due to vascular insufficiency. Some hemorrhage was observed in the area of necrosis, but this was not prominent. In some areas of fat necrosis in the peritoneal cavity, evidence of calcium deposition was seen microscopically.

The kidneys showed some very remarkable changes on cut section. They appeared enlarged and weighed about 140 grams each. The parenchyma of the kidney bulged somewhat above the cut surface. The cortices were extremely pale, as shown in Figure 3. Besides the changes in the cortex, this picture shows that the right kidney also contained another lesion. Arising from the upper pole of this kidney there was a cystic, yellowish, somewhat hemorrhagic lesion measuring 3½ x 2 cm, which projected towards the hilus of the kidney. Microscopic examination of this lesion showed a typical appearance of hypernephroma with large clear cells containing abundant cytoplasm and small eccentrically placed nuclei. In many areas these clear cells appeared to form glands, and this accounts for the large cystic areas seen grossly. Microscopic examination of the rest of the kidney showed patchy areas of necrosis of tubular epithelial cells. These cells did not, however, show marked vacuolization similar to that seen with Mannitol administration.

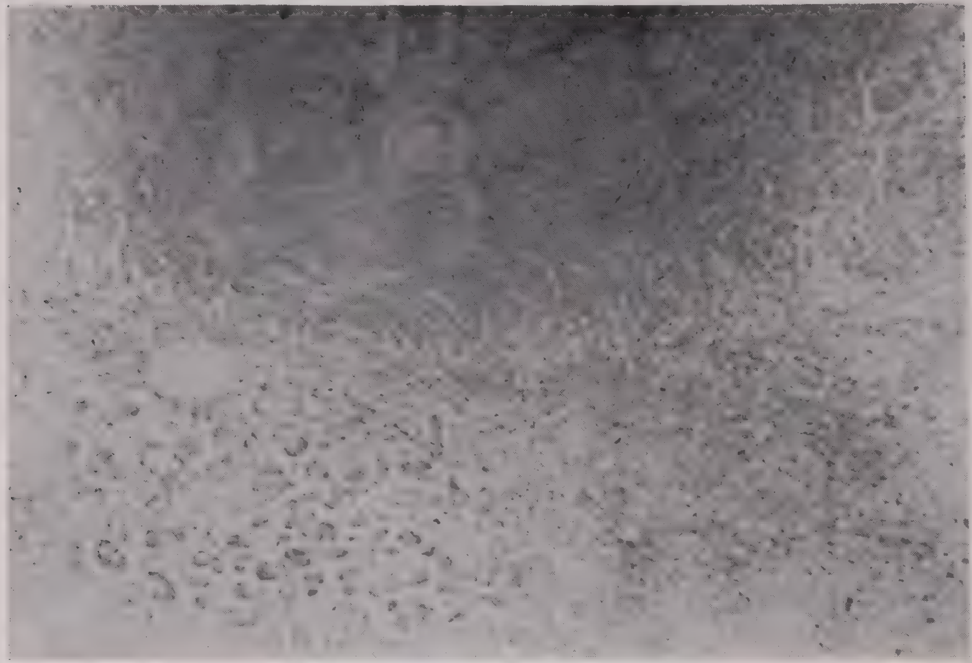

Fig. 2—Necrotizing Pancreatitis

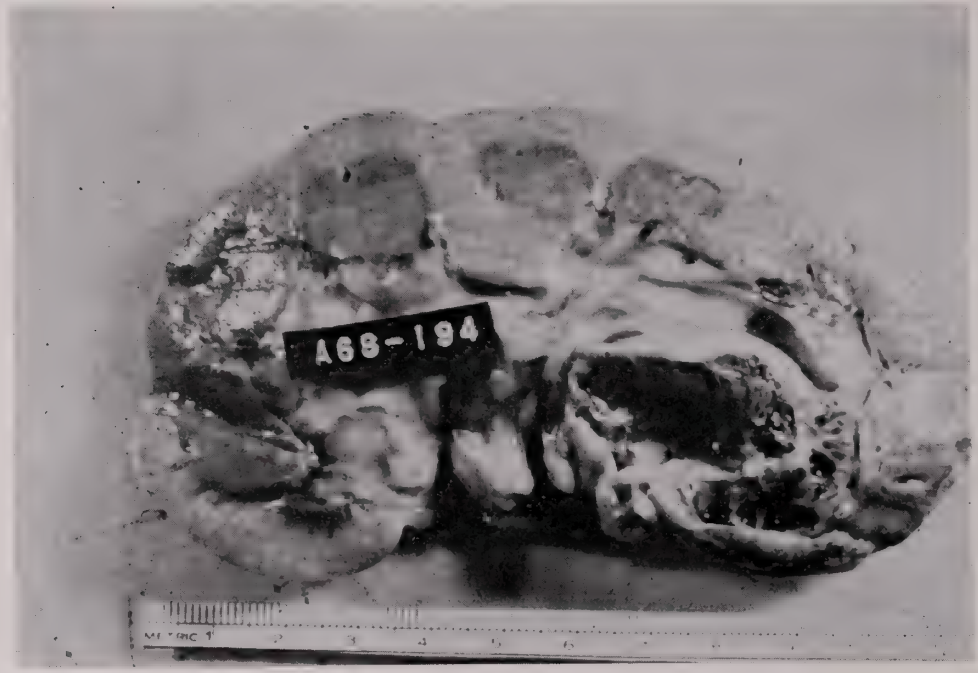

Fig. 3—Hypernephroma

Figure 4 shows a high-power view of several of the tubules which contain necrotic cells in the lumen. One tubule also shows the tubulorrhexic lesion that has been described by Oliver.[1] This consists of a disruption of the basement membrane of the tubule with loss of the contents of the tubule into the interstitial space. This is the lesion that is supposed to be characteristic of ischemic injury in contrast to the nephrotoxic lesion due to chemical injury in which the basement membrane remains intact. Other microscopic sections of the kidney show rather striking areas of interstitial edema without much evidence of inflammatory response. The glomeruli, arteries and arterioles appeared perfectly normal microscopically and showed no evidence of preexisting renal disease. In particular, there was no evidence of diabetic glomerulosclerosis. In reference to diabetes, it might also be mentioned that a few islets were found in the sections of pancreas, but these islets appeared perfectly normal and showed no evidence of hyalinization such as is seen in diabetes.

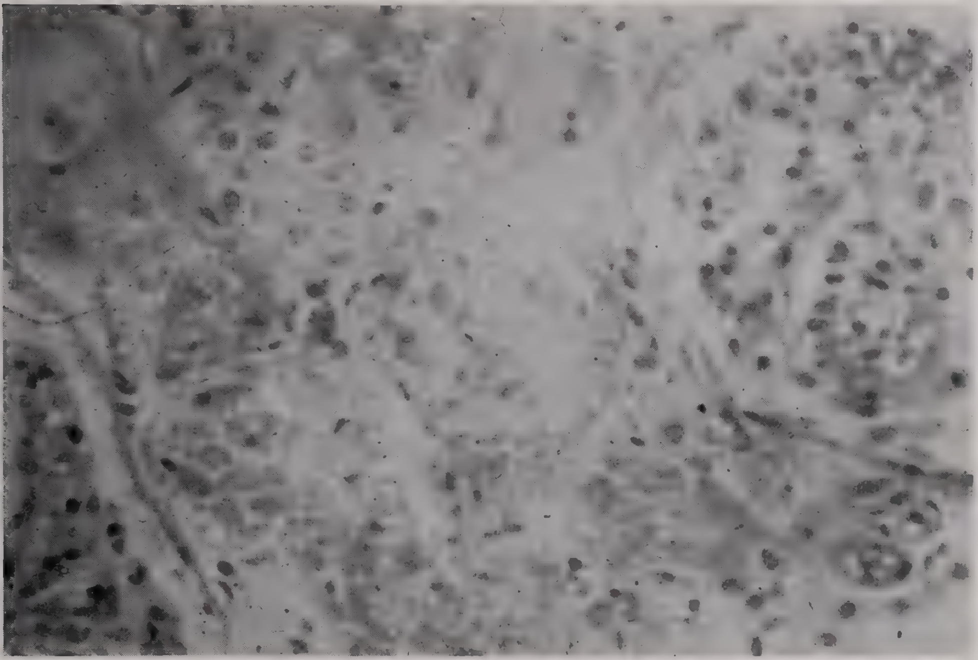

Fig. 4—Tubulorrhexis

The sections of liver showed extensive centrilobular necrosis. When the gastrointestinal tract was opened, large amounts of blood were present within the stomach, esophagus and duodenum, extending well into the small intestine. The stomach mucosa contained numerous small punctate ulcers. Microscopic examination of these ulcers showed them to be quite superficial, extending through the submucosa to the inner muscular layer but no further.

In the lungs, a 1 x 1.7-cm firm, hard nodule was present in the apical segment of the left lower lobe. On cut section this was somewhat elevated above the surface of the lung and was very white in appearance. Microscopic examination of this lesion revealed typical mature hyaline cartilage sharply demarcated from the surrounding lung. This was a typical benign hamartoma. There was also a 5-mm in diameter firm nodule present in the posterior aspect of the upper lobe of the left lung; there were also numerous tiny nodules present throughout the spleen. Microscopic examination of these lesions revealed partially calcified granulomata with only a few giant cells.

Special stains did not reveal any definite organisms, but these lesions certainly would be compatible with healed histoplasmosis. There was extensive bronchopneumonia present in the right lower lobe as well.

In the heart there was evidence of hemorrhage into one of the leaflets of the tricuspid valve; this was confirmed microscopically. There were also numerous punctate hemorrhages throughout the myocardium. Microscopically, these showed evidence of excessive amounts of red blood cells lying between the myofibrils without any significant surrounding inflammatory reaction. There was also gross and microscopic evidence of hemorrhage of the endometrium. The parathyroids were examined carefully and all appeared normal.

A recent article by Block and Priest[2] emphasizes that recurrent pancreatitis can be associated with multiple very small stones in the gallbladder. In their series, these stones were frequently too small to be seen radiographically. At the time of surgery these stones measured 1 to 2 mm in diameter. After removing the gallbladder with the stones, the patients had no further bouts of relapsing pancreatitis. Three of their five patients had definite choledocholithiasis. Stones in the biliary tract are often seen in cases with pancreatitis. In Blumenthal and Probstein's series, 10% of their cases had definite obstructive disease of the biliary tract. They emphasize in their classic monograph[3] that the opening of the duct of Wirsung must be at least 2 to 3 mm above the Ampulla of Vater to permit impaction of a small stone in the ampule without actually occluding the pancreatic duct. This situation was present in this case with the duct of Wirsung opening 4 mm above the Ampulla of Vater.

In their series of acute pancreatitis, about 60% of these cases were associated with antecedent evidence of chronic disease in the biliary tract. It has been shown experimentally that pancreatitis will result when a combination of bile and pancreatic juice is injected into the pancreatic duct. However, for hemorrhagic pancreatitis to be present, vascular occlusion also needs to be present. As mentioned earlier, the sharply demarcated areas of necrosis in this case might suggest a vascular role as well. A logical mechanism for this vascular occlusion would be production of thrombi in the smaller vessels supplying areas of the pancreas. This may be due partly to inflammatory reaction in the vessels and also partly to a hypercoagulable state which has been associated with pancreatitis.

In 1965, Nudelman and co-workers[4] showed that infusion of a bile and trypsin combination into the pancreatic duct in dogs produced an acute pancreatitis, whereas bile alone did not. They also further showed by the use of electron microscopy that a very early lesion produced by the bile-trypsin combination was the loss of micro-villi from the luminal surface of the acinar epithelial cells. As a result, foreign particles were readily ingested into the cells, whereas with micro-villi intact, the cells did not ingest foreign material.

There is one other possible etiology for the pancreatitis that might have existed in this lady. She did have very distinct xanthalasma. There have been cases of recurrent acute pancreatitis reported in patients who have significant hyperlipemia. In these cases, fat emboli may be the etiology. There were no lipid studies performed on this patient.

The association of acute tubular necrosis with acute pancreatitis has only recently been well appreciated. Taylor[5] in 1949 published 110 cases of acute pancreatitis and in only one of his patients was oliguria mentioned. However, in recent years there have been increasing reports in the literature indicating the not uncommon association of these two conditions. In 1962, Balslov[6] reported on 300 cases of acute renal failure in Denmark, 13 of which were due to acute pancreatitis. In 1959 there was a report by Beisel and co-workers of four cases of acute pancreatitis which developed acute renal failure.[7] In three of these, acute tubular necrosis was found; in one the renal failure was due to bilateral renal cortical necrosis.

It is emphasized in this article and in many others that the combination of acute pancreatitis and acute tubular necrosis is a particularly lethal combination. There is an 80% mortality associated with this combination in the literature. The mechanism for the development of acute tubular necrosis is probably the decreased renal profusion secondary to the shock that is present early in the disease. However, Lee and Hills[8] have recently reviewed evidence showing that the acute tubular necrosis is due to a release of some substance from the pancreas into the circulation. Other authors have implicated vasodilator substances, such as bradykinin in these situations.[9] There are other causes of acute renal failure in pancreatitis that have been reported. These are quite rare but probably should be mentioned. One is bilateral renal artery thrombosis; a second is fat emboli to the kidneys from areas of fat necrosis.

The nature of this patient's hemorrhagic diathesis is a bit difficult to elucidate. Reports in the literature vary markedly from a hypercoagulable state to a hypocoagulable state associated with acute pancreatitis. In 1963, Shinowara[10] demonstrated hyperfibrinogenemia and elevated Factor 8 concentrations in cases of acute pancreatitis. However, one has to be cautious in interpreting these elevated levels as being indicative of a hypercoagulable state. Wessler[11] has recently shown that it is important to know whether clotting factors are in an inactive or active form before one can say that a hypercoagulable state exists. It is known that trypsin activates conversion of prothrombin to thrombin, and this rapid conversion could conceivably lead to a hypercoagulable state.

Innerfield,[12] in 1951, found elevated antithrombin levels in 50 of 55 cases of acute pancreatitis. This would support the view that excess prothrombin was being converted to thrombin. It is also known that prothrombin times are often quite prolonged in acute pancreatitis. It thus seems quite likely that early in the course of pancreatitis a hypercoagulable state might exist, perhaps secondary to trypsin release into the circulation and its subsequent action on the prothrombin. As clotting factors are used up later in the course of the disease, a hypocoagulable state might readily exist: in other words, a consumption coagulopathy. This patient's prolonged prothrombin time and decreased fibrinogen terminally would substantiate this. Her prothrombin time could also have been prolonged secondary to the extensive centrilobular necrosis that was present in the liver.

Summary

The case is that of a middle-aged, obese woman who had numerous small gallstones present in the gallbladder, several of them in the common duct. She had a common drainage channel measuring 4 cm for the pancreatic secretions and the bile. Secondary to these findings, she developed a severe hemorrhagic and necrotizing pancreatitis. As a result of this hemorrhagic pancreatitis, she developed acute tubular necrosis and went into renal shutdown. She had numerous small gastric ulcers which led to massive

gastrointestinal hemorrhage and would account for the rapid terminal fall in hemoglobin.

There were also several interesting incidental findings: a hypernephroma of the right kidney; a hamartoma in the left lung; probable healed histoplasmosis involving the left lung and spleen; a bleeding diathesis which manifested itself by multiple skin ecchymoses, hemorrhage into the myocardium, and possibly hemorrhage into the tricuspid valve.

Dr. Shapiro:

Are these ulcers in the stomach the kind that you can see in patients who receive large amounts of Levophed?

Dr. Crosson:

We attributed the presence of the ulcers to her uremic state. I think Levophed might well have contributed, however.

Hugh Edmondson, M.D.*
John Crosson, M.D.†
Thomas Mulrooney, M.D.*
Minneapolis, Minnesota

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†Resident Department of Pathology, Hennepin County General Hospital.

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Tourniquet Paralysis Syndrome

Mechanical pressure from a tourniquet may cause both motor and sensory changes in the function of peripheral nerves. According to Moldaver, muscle paralysis may be present with either hypotonia or atonia although there is no evidence of atrophy. Sensory dissociation also occurs. The sensations of touch, pressure, vibration, and position are usually absent. Duration of impairment of both the sensory disturbance and motor function may be as long as three months or more.

Durham, Robert H.—Encyclopedia of Medical Syndrome
Hoeber Medical Division, Harper and Row, New York

Case Reports

Drug Fever Due to Procainamide

SINCE LEIBOWITZ in 1951[1] first described fever after the use of procainamide, a few more similar cases have been reported. They all resemble each other more or less, but the importance of *primum nil nocere* justifies the description of another case.

Case Report

History

A 64-year-old white man was admitted to Northwestern Hospital on April 12, 1968, because of chills, fever, headaches and muscular aching of two days' duration.

He had previously been admitted to the same hospital on March 24, and remained until April 6 of that same year with a complaint of dyspnea that he described as "choking and inability to get air." He stated that he had had a number of similar attacks over the preceding ten years. His history included hospitalization 27 years before for a "nervous breakdown." Other hospital admissions were for a tonsillectomy, hemorrhoidectomy, rectal fistula and herniorrhaphy years before. The patient also complained of life-long migraine headaches and sinus trouble.

Physical examination revealed a few moist crepitant râles in both lung bases and slight cardiac enlargement. A late blowing systolic murmur was heard best at the apex, with a muffled second sound (S_2). (A systolic murmur was first noted by his physician* in 1963). An electrocardiogram showed multifocal ventricular premature contractions and ST-T wave changes compatible with left ventricular ischemia. His circulation time arm to tongue was 22 and 19.5 seconds. All these findings suggested that he might have slight mitral incompetence, possibly due to a dysfunction of the posterior papillary muscle. Bronchoscopy performed on April 4, 1968, revealed a laryngospasm associated with chronic bronchitis. The patient was digitalized and given Pronestyl® (procainamide) 250 mg. four times daily and Valium® 5 mg. three times daily; these were commenced on March 25, 1968, and continued on discharge, April 6, 1968. At this time there were no premature ventricular contractions.

Physical Examination

On this second admission, April 12, 1968, the blood pressure was 132/74 mm. Hg., temperature 104° F., pulse 96/minute. The patient was shivering and having chills. There were moist crepitant râles in the left lung base. A grade III/VI late blowing systolic murmur was again heard best at the apex. There was no evidence of jaundice, adenopathy, enlarged liver or spleen, rash or petechiae. Examination of the joints showed no abnormalities.

Laboratory Data

The erythrocyte sedimentation rate was 28 mm. in the first hour; hemoglobin 14.8 g%; white blood cell count 8,000 cells/mm^3 with the following hemogram: 75% polymorphonuclear cells, 19% lymphocytes, 2% myelocytes, 3% eosinophils and 1% basophils. The prothrombin time was 14.2 seconds (control 12.7 sec.). The platelet count was 267,000/mm^3, and 1.4% reticulocytes. A lupus erythematosus clot test was negative on two occasions. Determinations of serum electrolytes and enzymes, including amylase, were within normal limits. On examination of blood from the ear lobe, no histiocytes were seen. Complement fixation tests were negative for histoplasmosis, blastomycosis, and coccidiomycosis. Serum total protein was 5.8 g% (3.3 g% albumin and 2.5 g% globulin). The serum bilirubin level was 0.1/0.6 mg%, the blood urea nitrogen 17 mg%, the uric acid 3.6 mg%. Urinalysis was negative; two of the 10 urine cultures grew out E. coli about 100,000/cc. Stool examinations showed occult blood trace to 2+. Serology was negative for paratyphoid A and B, Brucella, and Weil Felix Ox19. Blood cultures for aerobic and anaerobic organisms, as well as for fungi, were negative. Fluorescent antinuclear antibodies were not found. X-ray studies included the skull, an intravenous pyelogram, a cholecystogram, and the chest; no abnormalities were seen. An examination of the bone marrow proved normal. The spinal fluid contained no white or red blood cells; 83 mg% sugar; Pandy was negative. Electrocardiographic tracings showed atrial premature beats but no premature ventricular contractions.

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*We wish to thank Dr. Lyman Clay for referring this interesting case.

Course

The patient's temperature ranged from 99.2 to 104.5° F. for the first four days after his admission. During that time he was given 250 mg. procainamide four times daily, Valium® 5 mg. three times daily, and on seven occasions 650 mg. aspirin (ASA). After all medications were discontinued on the evening of April 15, the temperature returned to normal on the evening of April 16 and remained normal (Figure 1-a). Six days later he was given a test dose of 250 mg. procainamide by mouth. His temperature began to rise after six hours and reached a climax of 104.4° F. nine hours after application. Thirty hours after the test dose, the temperature returned to normal (Figure 1-b). The patient was discharged on April 30, 1968, and was seen May 13 in good condition and without any complaints.

Comments

If an otherwise unexplained fever occurs during administration of procainamide, it is essential to withdraw the drug and note whether the fever promptly remits. The patient described in this report had an acute febrile episode with no leukocytosis and negative studies for infection, leading to the suspicion that he might have a drug fever. Withdrawal of the drugs and subsidence of fever confirmed this suspicion. Recurrence of the fever after challenge of procainamide essentially established the diagnosis of fever due to procainamide (Figures 1-a and 1-b).

The origin of drug fever may be on an allergic basis, but the immunologic mechanism is still not clear. There are four different possibilities for the cause of fever in relation to drug administration: (1) nonspecific cause (impurities), (2) specific chemical effect, (3) Herxheimer's reaction, (4) allergic reaction with or without manifestations of cutaneous, vascular or gastrointestinal type. Fever secondary to the use of procainamide (Pronestyl®) is probably in the latter category.

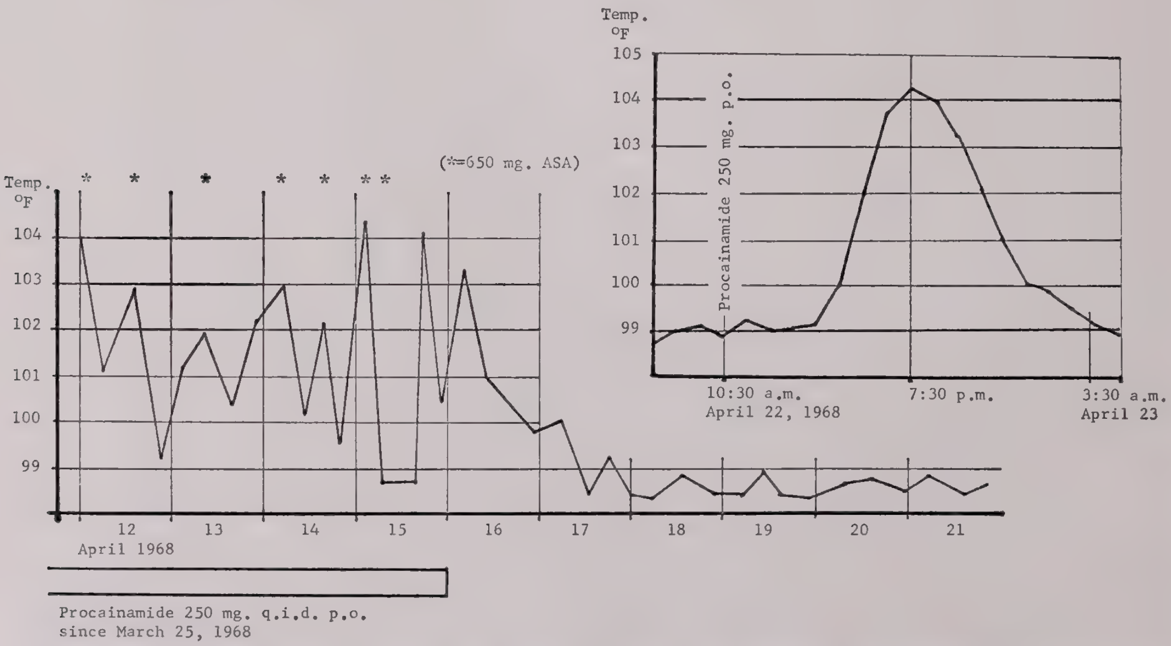

Fig. 1a—Temperature curve of patient with procainamide fever.

Fig. 1b—Provocation of procainamide fever by test dose.

This type of drug fever generally occurs one to two weeks after the onset of procainamide therapy in sensitive individuals. In our case and in the literature, no additional sensitivities to other drugs were noted. It is also interesting that several of the reported cases and our patient had tolerated procaine as a local anesthetic without adverse reaction. This allows the suspicion that the replacement of the ester linkage of procaine by an amide linkage not only leads to its more potent anti-arrhythmic effect but also enhances allergization.

A comparison of our patient with nine cases of procainamide fever previously described in the literature[1-7] is given in the Table. Other side effects to procainamide, such as skin rashes, agranulocytosis or connective-tissue diseases, including a lupus erythematosus-like syndrome,[8,9] were not observed in our patient. Although there are more cases reported with a lupus-like syndrome than with fever alone in connection with procainamide, the possibility cannot be excluded that in some of the latter cases fever might have been the first sign of a lupus-like syndrome. Adverse reactions to procainamide are obviously not very rare: Fakhro et al.[10] reported that fifteen out of fifty patients treated with procainamide showed one or more symptoms of the lupus-like syndrome.

The current, all too commonly practiced, polypharmacy, more often with rather new drugs, may be expected to lead to an increase of adverse reactions. Therefore it is most important to keep in mind the possibility of side effects of an administered drug to explain a patient's otherwise cryptogenic fever. In such cases, withdrawal of all drugs will promptly result in defervescence.

TABLE

Reference	Daily dose of Procainamide mg.	Onset of fever	Repeated provocation	Max. temp., °F	Lab. data, etc.	Case
(1) Leibowitz	4 × 500	within a week	× 1	104	ESR 7 mm	♂ 48y
(2) Bakos	6 × 250	after 10 days	× 2	104	WBC 5000	♀ 58y
(3) Hellman	6 × 250	same day	× 1	102	Eos. 1 → 7%	♂ 53y
(4) McGarry	6 × 500	after 8 days	× 1	105	skin rash	♂ 57y
(5) Luton	6 × 500 4 wks 1952	after 1 day 1957	× 3	101	1952 no reactions	♂ 61y
(6) King	(?) 1952	same day 1962	× 1	103	LDH ↑, SGOT ↑ alk p'tase → bilirubin →	♀ 78y
(7) Hey	a) 4 × 500 b) 5 × 500 c) 3 × 250	after 15 days 15 days 14 days	× 2 × 1 × 1	104 105 106	WBC 6300 WBC 7400 WBC 5100	♀ 35y ♂ 59y ♂ 75y
Our patient	4 × 250	after 16 days	× 1	105	ESR 28 → 41 WBC 8–9200 Eos. 1–8% LE neg. × 2	♂ 64y

Comparison of references from the literature to our case of drug fever due to procainamide.

Summary

A 64-year-old male patient demonstrated drug fever due to procainamide. Fever started 16 days after commencement of Pronestyl® therapy, 250 mg. four times daily by mouth. The day after discontinuance the temperature dropped to normal, but later rose briefly again after a single provocative dose of 250 mg.

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Housemaid's Knee

Awe of doctors and wonderment over their behavior is characteristic of the human race. We patients love to tell yarns tending to show that our doc is just a regular guy like anybody else, but we don't really believe it. And for good reasons.

Doctors know too much about us. Scrape an inch off one of them and you'll discover the world's darkest and dankest secrets piled in there. We have all told doctors things that we would not confess ordinarily even to ourselves alone in a room with the shades down and the door locked. We hold up our souls for their inspection. We also hold up every item of anatomy and, if the doctors can't find anything interesting on the outside, we let them poke around inside with flashlights.

Other circumstances set them beyond the pale. Though packed with medical knowledge, they dole it out as stingily as a man letting you smell the cork of his bottle of Napoleon brandy. For two years I have sought by cajolement, by trickery, by outbursts of temper, by sicking one doctor on another, to learn precisely what ails me. My impression to date is that I suffer from a mild form of housemaid's knee and I've abandoned hope of ever learning more.*

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*Sprague, Marshall: The Business of Getting Well, 1943.

Opinion of the Public

People come in three classes: the few who make things happen, the many who watch things happen and the overwhelming majority who have no idea what happened.—News, Woonsocket, S. D.

Grand Rounds

Adult Scurvy*

RAFAEL CARMENA, M.D.
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THE FIRST RECORDED accounts of scurvy are to be found among the writings of the physicians who accompanied the Crusades in the XIII century. Vasco de Gama, who sailed round the cape of Good Hope in 1498, described how a hundred of his crew of 160 perished from scurvy at sea. Scurvy ran an extremely high incidence among the crews of most maritime expeditions during the 16th and 17th centuries, and it was also seen on land, particularly during wars and in prolonged sieges. The main manifestations were "putrid gums, lassitude, pain in the knees, and skin hemorrhages," and it was soon realized that they could be prevented and treated by eating fresh fruits and vegetables. Sir Richard Hawkins' "Observations in the Voyage to the South Sea," published in 1593,[1] contains an account of the prevention and treatment of the disease with lemon juice. Jacques Cartier (1535), during his exploration to Canada and what is now northern Minnesota, found that the native Indians prevented the disease by drinking a decoction of pine needles, which we now know contain ascorbic acid.

In 1734 Bachstrom[2] wrote that scurvy should be attributed solely to a total abstaining from fresh vegetables, foods and greens, and not to cold climates, sea air, eating salted meat, etc. A few years later James Lind (1753),[3] an English ship's surgeon, published his "Treatise on the Scurvy," wherein, by means of dietetic experiments with 12 scurvy patients, he demonstrated that oranges and lemons were the most effectual remedies. By 1804 regulations were introduced into the British Navy, making compulsory a daily ration of lemon or lime juice to all British sailors. This led to the almost complete eradication of scurvy in the British Navy, and to this day the nickname "limies" is applied to British sailors.

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*Presented as a Medical Grand Rounds at Hennepin County General Hospital, March 5, 1968.

Scurvy was a subject of interest for several scientific investigators of the 19th century. Hirsch (1860),[2] in his "Handbuch der historisch-geographischen Pathologie," concluded: "Scurvy appears when a special ingredient is lacking in nourishment and the disease disappears as soon as this substance is administered." This concept may well have instigated the theory of nutritional deficiencies. It was also around this time (1883) that Barlow published his classic observations on infantile scurvy.

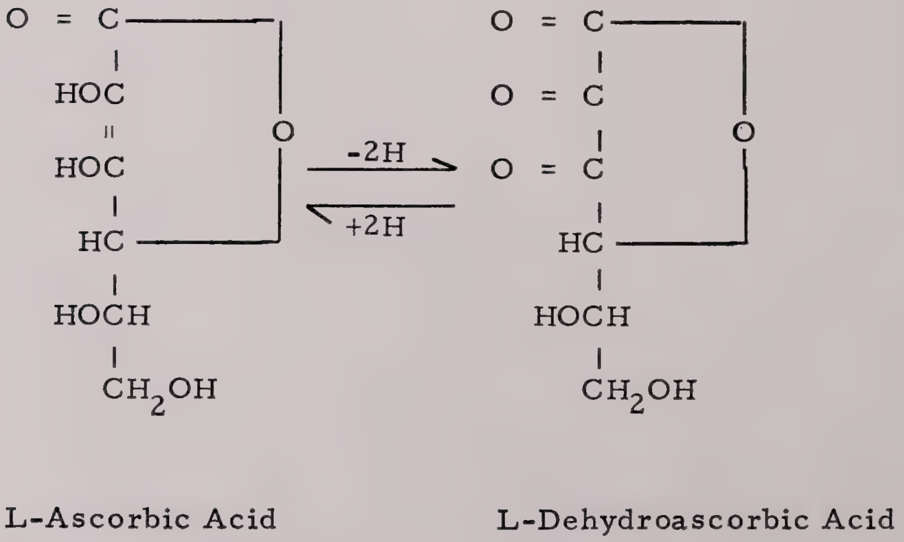
The era of experiments on nutrition began in 1881, when Lunin started animal experiments on the influence of diet on nutrition.[2] This lead to the discovery of polyneuritis gallinarum by Eykman in 1896, which founded the new theory of vitamins. In 1912, Holst and Frölich[4] fed guinea pigs exclusively on cereals and induced a disease essentially similar to scurvy, which could be cured by adding fresh vegetables and their extracts to the diet. The concept of vitamins was introduced by Casimir Funk in 1913. Diseases like scurvy, beri-beri and pellagra were called avitaminosis. The vitamin lacking in scurvy was called vitamin C.

In 1928 Szent-Gyorgyi[5] isolated from adrenal glands and cabbage leaves a crystalline substance which had an acid reaction and possessed strongly reducing properties. He called this substance hexuronic acid; but it was not until 1932 that hexuronic acid was identified with vitamin C and renamed ascorbic acid.

Chemistry

The structural formula of vitamin C was established in 1933 as a result of the work done by Haworth, Hirst and co-workers.[6]

Ascorbic acid forms colorless crystals which are freely soluble in water. It is a strong reducing agent and is therefore readily oxidized. The first oxidation product is dehydroascorbic acid, which can be reduced to ascorbic acid by hydrogen sulphide, cysteine and glutathione. Dehydroascorbic acid is as potent an antiscorbutic as ascorbic acid itself (Figure).



Figure

Biochemistry and Physiology

Species Specific

The only species for whom ascorbic acid is a vitamin are the primates, the guinea pig, an Indian bat and a bird (the red vented bulbul). These species depend exclusively on dietary sources for vitamin C since they lack the enzyme required to carry on the reaction from keto-gluconolactone to ascorbic acid.

Source

Good dietary sources of ascorbic acid are fresh fruits (strawberry, orange, lemon, grapefruit) and fresh vegetables (brussel sprouts, cauliflower, cabbage, tomato, potato). It is generally absent from dried, canned or preserved foods unless the process is carried out anaerobically. However, freezing or dehydration retains the vitamin. Vitamin C is lost during the cooking of vegetables by too much cooking water, over-cooking, etc. Foods devoid of vitamin C include meat, fish, eggs, fats and oils, and cereal products (Table 1).

Absorption

Ascorbic acid is absorbed from the small intestine by a simple diffusion mechanism, the rate of absorption varying directly within the concentration of ascorbic acid ingested. Under normal conditions intestinal absorption of ascorbic acid from the intestine is almost complete, because as shown by Farmer et al.[7] on normal intakes the fecal excretion is negligible. Under abnormal conditions (diarrhea, achlorhydria) intestinal absorption of ascorbic acid may be incomplete.

After absorption, ascorbic acid diffuses freely from blood to all body tissues. The major part of vitamin C lies inside the cells, not in the plasma or fluids. Normal human plasma contains about 0.5-1.5 mg. of ascorbic acid per

TABLE I
Ascorbic Acid Content of Some Fruits
Data from Bicknell and Prescott[1]

Fruit	Ascorbic Acid in mg. per 100 Gm. or 100 ml.
Apple	8
Grapefruit, juice	50
Lemon, pulp	15
Lemon, peel	150
Lemon, juice	70
Lime, juice	60
Orange, juice	80
Orange, Navel	90
Orange, Jaffa	40
Orange, Valencia	90
Tangerine, juice	50
Cabbage, raw	100
Cabbabe fresh, boiled 10′	45
Cabbage fresh, boiled 60′	15
Cabbage fresh, boiled 90′	5

100 ml.; RBCs contain about twice as much, and WBC and platelets contain 20 to 40 times more than plasma.[8] The adrenal cortex and the anterior pituitary contain more than any other organ or tissue in the body.

Metabolism

The vitamin exists in the body largely in the reduced form (ascorbic acid) in reversible equilibrium with a relatively small amount of dehydroascorbic acid (oxidized form). Ascorbic acid is partially destroyed and partially excreted by the body. It is believed that on a daily intake of 100 mg. about 50 percent undergoes metabolic conversion to CO_2 (excreted by the lungs) and oxalic acid (excreted in the urine). It is also excreted as ascorbic acid in the urine, the total amount being some 20 mg. in 24 hours.

There is no evidence that any particular organ or tissue serves as a storage reservoir for vitamin C. However, the body probably does have mobilizable reserves of ascorbic acid since clinical manifestations of scurvy develop in man only after several months of being on an ascorbic acid-free diet. It has been estimated[9] that the total vitamin C content of the human body when fully saturated ranges between 4 to 6 Gm., of which perhaps 200 mg. is present in the plasma and extracellular fluid, and the rest within the cells.

There is a renal threshold for vitamin C excretion. The vitamin is excreted by the kidneys in large amounts only when the plasma levels exceed this threshold, which is approximately 1.4 mg.%. Therefore, when the body is saturated with ascorbic acid, the plasma level will be approximately that of the renal threshold; when further amounts of vitamin C are administered most of it escapes into the urine. When the tissues are not saturated and plasma level is low, the ingestion of ascorbic acid results in little or no renal excretion. This is the basis for the so-called "saturation test."

Function

The precise functions of ascorbic acid in tissue metabolism are totally unknown; so also are the biochemical lesions which cause scurvy. Vitamin C stimulated more inquiry than perhaps any other vitamin, but we have not yet gotten an answer as to what it does in the body. Following is a short list of the metabolic functions vitamin C is probably related to.

Tissue Oxidation and Reduction

Shortly after its discovery it was thought that the main role of ascorbic acid was to act as hydrogen acceptor in tissue oxidation mechanisms. However, we lack any good evidence of this, and most investigators now agree that ascorbic acid acts probably as an anti-oxidant by providing a supply of readily available hydrogen. This goes along with the fact that vitamin C is present largely in the body in the reduced state (ascorbic acid) and only a small part in the oxidized form (dehydroascorbic acid). Thus, ascorbic acid may play an important role in keeping SH-activated enzyme systems in their reduced state.

Tryosine Metabolism

It is well known that scurvy patients metabolize tyrosine incompletely when given extra amounts of this amino acid.[10,11] This led to the discovery that ascorbic acid protects the enzyme p-hydroxyphenylpyruvic acid oxidase from inhibition by its substrate, but does not act as a cofactor for that enzymatic step. Moreover, other reducing agents have been shown to be equally effective in "protecting" the same enzyme.

Bone and Connective Tissue Metabolism

The synthesis of collagen requires ascorbic acid.[12] It has also been shown that scorbutic guinea pigs not only fail to synthesize new collagen fibers but show a rapid collagen degradation. Although the synthesis of collagen is a very complex matter and not totally understood as yet, present evidence suggests that ascorbic acid may intervene in the conversion of proline to hydroxyproline, before the synthesis of the peptide chain. Hydroxyproline is not synthesized in the absence of ascorbic acid, and it is important to remember that exogenous hydroxyproline is not incorporated into collagen.

Ascorbic acid is also essential for the formation of bone and cartilage; the proper functioning of osteoblasts and odontoblasts depends on it. In scurvy, bone formation ceases; hence the typical low serum alkaline phosphatase values. The osteoblasts are unable to synthesize osteoid and become surrounded by liquid with a region of edematous connective tissue appearing at the end of the diaphysis. In growing bones, subperiosteal hemorrhages frequently occur. Fractures heal slowly, as do wounds.

Adrenal Glands

No other organ in the body contains as much ascorbic acid as the adrenal cortex (about 5 mg. of ascorbic acid per gram of dried tissue). However, we simply do not know what ascorbic acid does in the adrenal. There is no evidence that it is involved in the synthesis of cortical hormones. Patients with scurvy have normal adrenal function, and patients with Addison's disease do not develop scurvy.[10]

*Erythropoiesis**

Anemia (of no particular type) is frequently seen in cases of scurvy and is usually corrected by the administration of ascorbic acid alone. Although this is still a controversial problem, most investigators now agree: (a) *Ascorbic acid plays some role in the metabolism of folic acid;* it seems to be essential for the conversion of folic acid into its active form, folinic acid (citrovorum factor). This has recently been questioned by Cox et al.[13] who found no evidence for that theory but concluded that ascorbic acid is indeed involved in the protection of folic acid reductase, maintaining a higher concentration of folic acid coenzymes. (b) *The transfer of plasma-bound iron into the liver and its incorporation into ferritin in this tissue requires the presence of ascorbic acid.* Since ascorbic acid is rather specific for this reaction and cannot be replaced by other reducing agents this could well represent a unique biochemical function for vitamin C.[14]

Cardiovascular System

It has been shown[15] that the peripheral vascular system requires vitamin C to maintain its responsiveness to stimulation with epinephrine. Ascorbic acid is involved in the maintenance of good capillary tone and resistance. It is also known[16] that patients with scurvy may develop electrocardiogram abnormalities (prolonged PR, elevation of ST) that are corrected by the administration of ascorbic acid. This leads to a topic that has received particular attention from Russian investigators: the effects of vitamin C on serum lipids. According to Miasnikova and Tiapina[17] high doses of vitamin C (500 mg. I.V. daily) would reduce serum cholesterol and improve the clinical status of patients with myocardial ischemia. However, the recent work of Samuel and Salchi[18] has failed to confirm this.

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*See Test Your Word Score Page 759.

Other Possible Functions

Ascorbic acid has been implicated in many different body processes: carbohydrate metabolism, formation of antibodies, activity of serum complement, phagocytosis, detoxicating function, etc. However, we lack good experimental evidence to support any such theory.

Clinical Manifestations of Scurvy

Under Experimental Conditions

There are three stages in the development of experimental scurvy in humans:[9,19] (1) initial stage, with changes in the vitamin content of the blood and no clinical signs; (2) clinical scurvy, with changes in the skin, gums and impaired wound healing; (3) final stage with hypotension and danger of death. Our present knowledge is based mainly on the work of Crandon[9] who induced scurvy in himself and on the Medical Research Council experiment[19] in 1948.

Symptoms of scurvy appeared after about 150 days on a vitamin C-free diet. They consisted of keratosis of the hair follicles in the skin and perifollicular hemorrhages. After six months, swelling and hemorrhages of the gums appeared, and wound-healing processes were affected. Later on, signs of cardiac ischemia and peripheral collapse may appear, together with loss of neuromuscular coordination and marked asthenia, forcing the end of the experiment. No anemia, bleeding, weight loss or susceptibility to infection were noted.

Naturally Occurring in Adults

Most cases are encountered among old men living alone ("bachelor scurvy") whose diet is grossly imbalanced and devoid of sources of ascorbic acid. Ignorance, apathy, alcoholism and poverty are the usual basis for its development. In some cases scurvy is only one of the many manifestations of malnutrition. A fair number of cases have been reported among people with gastrointestinal disturbances (peptic ulcer, diverticulosis, chronic cholecystitis) who were advised to avoid fruits and vegetables and followed the advice too drastically. It is worth noting that the Sippy diet affords a daily intake of vitamin C of only 0.5 mg.,[20] obviously not enough to cover the daily requirements.

Adult scurvy tends to appear more commonly in the spring, reflecting the relative lack of fresh fruits and vegetables during the winter months. The most frequent clinical manifestations are:

1. Malaise, weakness, lassitude
2. Perifollicular hemorrhages (abdomen, thighs and forearms)
3. Petechiae and ecchymoses
4. Swollen and bleeding gums with loss of teeth
5. Anemia, leukopenia
6. Mental confusion
7. Postural hypotension and syncope
8. In fatal cases, vomiting and "addisonian crisis" precede death.

Cutforth[21] has reported 11 cases of adult scurvy seen in a teaching hospital in London over a six-year period. There were ten men and one female; the average age was 65 years; and all but one were living alone, on diets of tea, toast, bread and butter, meat and fish-paste sandwiches. Three of the patients had a previous history of duodenal ulcer and were purposely avoiding fruits and vegetables. All of them had been eating the above diet for a period longer than six months prior to admission. The characteristic manifestations are recorded in Table 2.

TABLE 2

Symptoms Found in 11 Patients with Scurvy[21]

Symptom		Number of Patients
Bruising		11
Extensive spontaneous extravasation present in six of them		
Anemia		9
Normocytic normch.	5	
Macrocytic	4	
Pain in limbs		8
Anorexia		8
Lethargy		6
Purpura		6
Hyperkeratotic hair follicles		6
Swollen gums		2

(Seven of the cases were edentulous)

Ascorbic acid in doses of 600 mg. daily was given to all the patients. Five received a standard ward diet, ascorbic acid and no other medication; the remaining six were given ferrous sulphate and vitamin B complex as well as ascorbic acid. All cases responded immediately to therapy; the purpura and smaller bruises were gone within one week and the hemoglobin levels became normal within a month. There was no difference in the response of the two groups.

Chazan and Mistilis[22] reported seven cases of adult scurvy seen at Boston City Hospital during a one-year period. The average age was 65 years; six were single men living alone. All gave a history of poor dietary intake; none could recall having eaten fresh fruits or vegetables for at least six months prior to admission.

Symptoms

Ecchymosis

Tables 3 to 5 show the most important symptoms, physical findings and biochemical data. It is worth noting that a huge ecchymotic area on a lower limb was the outstanding complaint in three instances. Five of the patients had a relatively low blood pressure. In fact, two of the patients had sudden, profound hypotension with no response to therapy and died. Post-mortem examination failed to reveal an immediate cause of death.

Low Blood Pressure

The work by Crandon[9] in 1940 showed that low blood pressure in human experimental scurvy was not due to blood loss or reduction in blood volume. It was easily corrected by administration of ascorbic acid. The only explanation we have so far for the hypotension encountered in human scurvy is that the peripheral vascular system becomes less responsive to epinephrine and more prone to vascular collapse and shock. There are experiments in scorbutic animals[1] suggesting that relative adrenal insufficiency may be responsible for the hypotension; but this observation has not been substantiated in man.

Anemia

The incidence of anemia in scurvy has been the subject of numerous papers ever since Mettier, Minot and Townsend[23] gave the first detailed account in 1930. According to recent reviews, anemia is quite common in adult scurvy. Goldberg,[24] reviewing 55 cases of scurvy seen at the Western Infirmary in Glasgow over a 23-year period, found that 49 (89%) of them had hemoglobin values below 12 Gm. on admission. Cutforth[21] found anemia in nine out of eleven patients with scurvy; Shafar[25] has reported severe anemia in two of the three cases seen over eight months at a public hospital. Chazan and Mistilis[22] found anemia in all seven patients reported, the condition being severe (hematocrit values below 23%) in four of them. Recently Cox et al.[13] and Asquith[27] have reported several cases of anemia in patients with scurvy.

There are three factors to which the anemia of scurvy has been attributed: (1) loss of blood (from the gut or into the tissues); (2) lack of blood forma-

TABLE 3

Summary of the Presenting Symptoms. Data from Chazan and Mistilis[22]

Case No.	Weakness and Lassitude	Weight Loss	Anorexia	"Red Spots" on Arms and Legs	Swelling and Ecchymosis of Extremities	Syncope Dizzy Spells	Painful Gums
I	+	+	+	+	+	0	0
II	+	+	+	+	+	0	+
III	+	0	+	0	+	0	0
IV	+	+	0	+	+	+	0
V	+	+	0	+	0	0	0
VI	+	+	+	+	0	0	0
VII	+	+	+	+	+	+	0

Note: + = present; 0 = absent.

TABLE 4

Summary of the Physical Findings on Admission. Data from Chazan and Mistilis[22]

Case No.	Pulse (beats/min.)	Blood Pressure (mm. Hg.)	"Cork-screw Hairs"	Perifollicular Hemorrhages	Hyperkeratosis of Hair Follicles	Gum Changes	Ecchymoses	Capillary Fragility Test	Infection
I	84	100/60	+	+	+	+	+	0	0
II	110	110/55	+	+	+	+	+	+	Tuberculosis
III	84	130/70	0	0	0	0	+	0	0
IV	80	110/60	+	+	+	+	+	0	0
V	80	104/70	+	+	+	+	0	0	0
VI	78	110/60	+	+	+	Edentia	0	0	Pneumonia
VII	88	115/70	+	+	+	Edentia	+	+	0

tion; and (3) increased blood destruction. It is quite clear now, however, that the first factor is of little importance. Cutforth[21] found no correlation between the severity of the anemia and the degree of extravasation of blood into the tissues. Goldberg and Cox[24] have reported consistently negative tests for occult blood in feces in all their patients with scurvy, and the same was reported by Chazan and Mistilis. The last two factors (lack of blood formation and increased blood destruction) have been supported by clinical and experimental observations. As was mentioned, ascorbic acid is related to folic acid metabolism and to the intestinal absorption of iron and the transfer of iron to the ferritin form. It has been shown that blood transfused into scorbutic patients survived poorly. By using 51-Cr, Goldberg[24] demonstrated increased hemolysis in four of six scorbutic patients with anemia. The hemolytic process was corrected by the administration of ascorbic acid.

In summary, the anemia of scurvy is multifactoral in origin; and in the adult it conforms to no particular type: it may be normocytic or macrocytic, normochromic or hypochromic. In the majority of cases that we have reviewed, the anemia was of the macrocytic normochromic type and there was a high reticulocyte count initially. WBC and platelets are usually normal. The bone marrow is generally hypercellular. The serum Fe and IBC are normal or low.

In most cases the anemia is corrected by the administration of ascorbic acid alone. Folic acid sometimes provides benefit, the same as iron. It is evident that chronic general malnutrition, chronic liver disease, chronic infection and external blood losses complicate the type of anemia seen in scurvy and also complicate the therapy. In conclusion: ascorbic acid deficiency has a deleterious effect on blood formation. Whether this is a direct or an indirect effect through interference with folic acid metabolism has not been determined.

Mental Changes

Finally, striking mental changes have been reported in scurvy: confusion, depression and lethargy. They were noted by Cutforth[21] in more than half of his patients. As a rule, all mental changes clear up rapidly with the administration of ascorbic acid.

TABLE 5
Biochemical Data. Chazan and Mistilis[22]

Case No.	Plasma Ascorbic Acid (mg. %)*	Serum Folic Acid (mμg./ml.)**	Serum Vitamin B_{12} Levels ($\mu\mu$g./ml.)f	Serum Iron Level (μg. %)ff	Serum Bilirubin (mg. %)	Urine Urobilinogen	Stool Guaiac Test for Occult Blood
I	0.03	5.0	539	64	3.3	1:32	0
II	0.00	....	....	29	2 2	....	0
III	0.18	3.6	400	66	....	....	0
IV	0.12	1.5	160	75	1.6	1:16	0
V	0.05	1.5	2,027	174	....	....	0
VI	0.00	....	....	67	....	....	0
VII	0.05	2.7	170	81	2 4	1:64	0

Diagnosis

The clinical diagnosis of scurvy is based upon the combination of poor dietary history, presence of hyperkeratosis of the hair follicles, perifollicular hemorrhages, ecchymosis and typical gum changes. The differential diagnosis should include the *purpuras* (low platelet count, prolonged bleeding time and clot retraction, drugs, fever and blood cultures for subacute bacterial endocarditis, lupus erythematosus preparations, etc.) ; *dilantin toxicity* may have similar gum lesions but gingivitis due to ascorbic acid deficiency seldom occurs without other florid manifestations of scurvy; *rheumatoid arthritis* also gives swollen joints but not bloody joint effusions; moreover the scorbutic patient will not have deformities such as are common to rheumatoid arthritis.

The following is an outline of laboratory diagnostic aids that should be used to confirm the clinical diagnosis:

Ascorbic Acid Levels in Blood and Urine

The plasma level of ascorbic acid falls too rapidly after the vitamin is removed from the diet and is of no diagnostic value. According to Crandon,[9] ascorbic acid levels in plasma fell to zero after 41 days of ascorbic acid deprivation, and signs of scurvy did not appear until day 134. Therefore, the plasma ascorbic acid level indicates the state of ascorbic acid nutrition for the preceding few weeks. A plasma level of 0 mg.% is compatible with but not diagnostic of scurvy. If ascorbic acid has not been administered previously, any amount of ascorbic acid found in plasma is incompatible with the diagnosis of scurvy.

The ascorbic acid level in the white cell-platelet layer (buffy coat) has diagnostic significance. Normal values are 25-40 mg. per 100 Gm. The buffy-coat level reaches zero after 125 days of ascorbic acid deprivation, paralleling the onset of scorbutic lesions. As Vilter[26] has stated, a value of 0 mg.% in the buffy-coat is the only laboratory evidence of scurvy.

Ascorbic acid almost disappears from the urine even before the level in the plasma is zero. Therefore, a low level of ascorbic acid in urine has the same significance as a low plasma level: it will make a diagnosis compatible but no more. This applies to a single collection as well as a 24-hour collection.

Saturation Test

This test depends upon changes in the urine and plasma ascorbic acid levels after an appropriate test dose. The usual technique is: (1) Administration of 100 mg. of ascorbic acid by intravenous injection; and (2) Determination of urinary excretion of ascorbic acid during the next three hours. A normal, well saturated person will excrete 50% of the test dose; a depleted person will excrete 15% or less, and a scorbutic person will excrete less than 5% of the test dose.[26] The test indicates only that a person's tissues are saturated or unsaturated. The results can be compatible but never diagnostic of scurvy. This is due to the fact that the kidneys will reabsorb most of the vitamin when the tissues are at all unsaturated.

Other Tests

Test for capillary fragility, x-ray of the bones, increased tyrosil derivatives, etc., have been used but are not diagnostic. It is of importance to mention that in infantile scurvy x-rays are the most helpful tool for the diagnosis.

Treatment and Prevention of Scurvy

Ascorbic acid is the specific therapy for scurvy. The vitamin is usually administered by the oral route but it may also be given by intramuscular or intravenous injection. The tablets are available in 25, 50 or 100 mg. of the vitamin; the solution usually comes in 100 mg. per 5 ml. In the majority of cases of scurvy, 100 mg. of ascorbic acid daily and a well balanced diet are enough to produce rapid cure. The dose should be increased in the presence of tuberculosis, pregnancy, lactation, malignancies or hyperthyroidism, conditions where the daily requirements for vitamin C are increased. One gram of ascorbic acid may be administered daily until the symptoms are under control. There is no evidence of toxic effects from large doses of vitamin C.

The estimated daily requirements of vitamin C vary according to different sources. The National Research Council of the U. S. recommends a daily allowance of 70 mg. The British Medical Association has stated that a daily intake of 30 mg. of vitamin C would provide a good margin of safety. Their statement is supported by the experiment conducted in 1948 with 20 volunteers where seven of them were kept fit on a daily intake of only 10 mg. of ascorbic acid; moreover, six individuals in whom scurvy was induced in this experiment were relieved of the disease by the same daily dose. The question remains though as to whether this daily intake which obviously prevents scurvy is enough. It is, in any case, insufficient to maintain the body in a state of full saturation. In animals which are capable of synthesizing vitamin C the vitamin content in the different organs has a constant value, i.e., they are saturated.[2] It would appear then that the state of saturation is the most favorable for man as well.

References may be secured from the Grand Rounds Editor.

The Campbells Are Coming*

The lilting melody of the song, "The Campbells Are Coming," is that of an old Irish folk song—subsequently appropriated by the Scotch to narrate the rousing exploits of their hero, John Campbell.

"The Campbells are comin', o-ho o-ho,
The Campbells are comin' to bonnie Lochleven."

The verses go on and on.

Who were the Campbells? Whence were they comin' and when and why?

The Campbells were stout-hearted loyalists (English and Scottish) who, under John Campbell in 1715, assembled in the Highlands to engage and rout the Jacobites (rebelling Scots) at Sheriffmuir in the Midlothian region of southern Scotland.

John, titled 2nd Duke of Argyll, was one of the illustrious Campbells, a long and historic line of Scottish earls and dukes: patriots, statesmen, soldiers, administrators. Not only do the annals of history assure John's name and fame; fiction too has immortalized him as one of the heroic characters in Sir Walter Scott's "Heart of Midlothian."

The melody is that of an old Irish folk song, "An Seanduine" (meaning "old man"). There had been several variations of this song until its first publication about 1745. Other printings followed in 1747, 1756, and 1761. Somewhere in this period the Scotch appropriated the melody, and it became "The Campbells Are Coming" with certain variants. The standardized version was produced by the Scottish musician Finlay Dun in the early part of the nineteenth century.

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*See editorial page 751.

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brand of tybamate

(When you consult
the Prescribing Information
you may agree
it makes good sense)

PRESCRIBING INFORMATION

Indications: Tybatran (tybamate) has afforded symptomatic improvement in a variety of psychoneurotic disorders, especially in the treatment of the anxiety and tension components of psychoneuroses. Anxiety states manifested somatically have responded to Tybatran (tybamate).

Tybatran (tybamate) has been useful in the control of agitation in the aged and in the alleviation of some of the adverse emotional accompaniments of senility.

Tybatran (tybamate) has been used with benefit in the treatment of depressive symptoms associated with anxiety and other symptoms of psychoneuroses. However, it is not indicated for primary treatment of depressive states. It is not an antipsychotic agent, although it has been used as adjunctive therapy in some psychotic patients.

Dosage: One 350 mg. capsule, 3 times daily and two at bedtime is suggested as the adult starting dose. Adjust to suit individual requirements. Daily doses above 3000 mg. are not recommended.

Contraindications: Known hypersensitivity to tybamate. Since no studies have been done with this drug in human pregnancy, it should not be used in pregnancy unless the potential benefit outweighs the risk.

Warnings: Administer cautiously to patients receiving phenothiazines or other CNS depressants or having history of convulsive seizures (See Adverse Reactions). Consider possibility of additive actions with alcohol or other psychotropic agents, particularly phenothiazines or MAO inhibitors.

Precautions: Avoid abrupt withdrawal after prolonged use, although withdrawal symptoms have not been reported to date. Exercise caution in addiction-prone individuals. If symptoms of hypersensitivity occur, discontinue at once and initiate appropriate symptomatic treatment. Avoid activities requiring optimal mental alertness if drowsiness or vertigo are present. As with any new drug, use cautiously in patients with history of drug allergies, blood dyscrasias, and hepatic or renal disease; periodic measurements of hepatic, hematopoietic and renal function should accompany prolonged and/or high doses.

Adverse Reactions: Most frequent reactions, rarely requiring discontinuation of tybamate, include drowsiness, dizziness, nausea, insomnia, and euphoria. There have been a few reports of skin rash, urticaria, and pruritus. Rare side effects include hyperactivity, fidgetiness, flushing, and tachycardia, suggesting excessive stimulation; also ataxia, unsteadiness, confusion, feeling of unreality, "panic reaction," fatigue, headache, paresthesias, vertigo, gastrointestinal disturbances, glossitis, and dry mouth. Grand mal or petit mal seizures have been reported in a few hospitalized psychotic patients receiving tybamate (up to 6000 mg. daily) together with phenothiazines and other psychotropic agents, but not with tybamate alone. Consider the possibility of rare, serious adverse reactions such as may occur with the related drug, meprobamate. If excessive amounts are ingested, gastric lavage and symptomatic therapy, including central stimulants as necessary, are recommended. Before prescribing, consult package circular.

Supply: Tybatran (tybamate) is available in green, sealed capsules of three strengths: 350 mg., 250 mg., and 125 mg. Each strength is supplied in bottles of 100 and 500.

A. H. Robins Company, Richmond, Va. 23220
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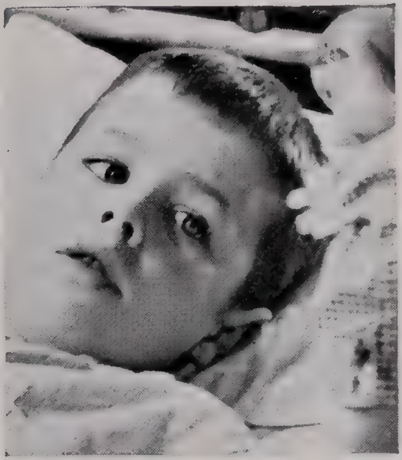

Save him from
RHEUMATIC FEVER

Here are two ways:

1. If your child has a bad sore throat, don't wait – it might be "strep." Call your doctor. Treatment of "strep" infections usually can prevent rheumatic fever and the heart damage it sometimes causes.

2. Give to your Heart Fund. Your Heart Fund dollars support research and community service programs which can wipe out rheumatic fever and save thousands of young lives.

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so more will live
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Arlidin is well tolerated and relatively free of severe adverse reactions.

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WORKSHOP SESSION '69

116th Annual Meeting

Convention Hall
Minneapolis

Time Table for Workshops

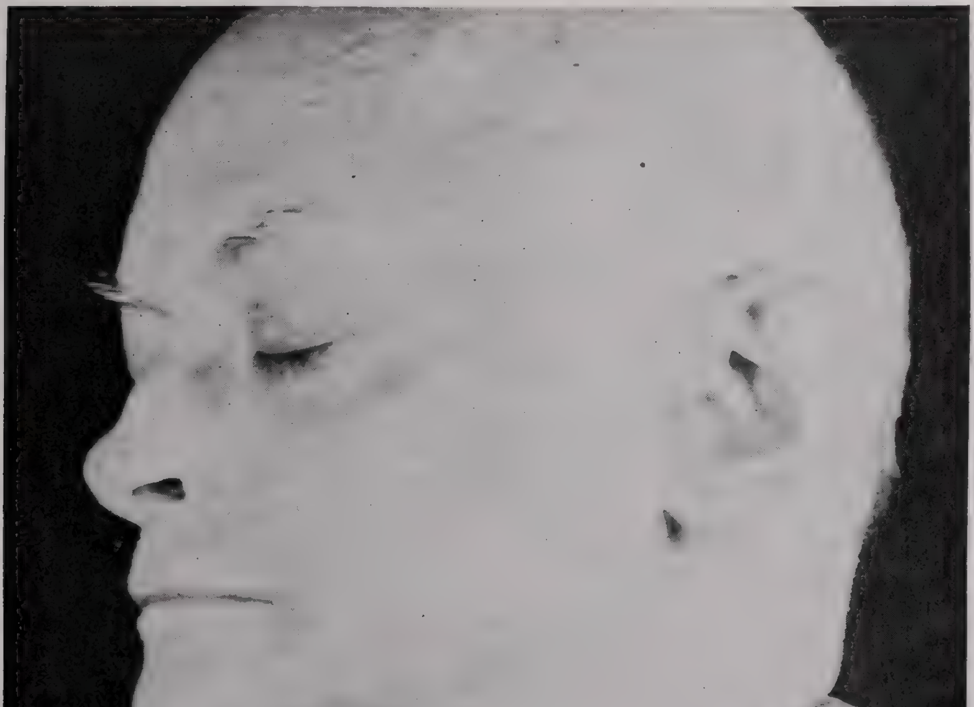
HOUR	Monday, May 26	HOUR	Tuesday, May 27	HOUR	Wednesday, May 28
Workshops given simultaneously. Each topic presented twice. First time: 2:00 to 3:00 p.m. Second time: 3:45 to 4:45 p.m.	"What to Do Until the Psychiatrist Comes" Thomas Burton Minneapolis	Workshops given simultaneously. Each topic presented twice. First time: 2:00 to 3:00 p.m. Second time: 3:45 to 4:45 p.m.	"Children Who Don't Grow" A. B. Hayles Rochester	Workshops given simultaneously. Each topic presented twice. First time: 9:30 to 10:30 a.m. Second time: 11:00 to 12:00 p.m.	"Prevention of Rh Disease" H. F. Polesky E. B. Berglund A. R. Thelemann Minneapolis
	"Anesthesia and Pulmonary Disease" Hugh D. Westgate Minneapolis		"Anesthesia and Patient Monitoring" J. J. Buckley Minneapolis		"Computer Applications in Medical Practice" J. A. Hilger St. Paul
	"Drugs for Nervousness?" Burtrum Schiele Minneapolis		"Thyroid Disease—A Therapeutic Controversy" A. L. Schultz F. C. Goetz F. Raymond Keating O. H. Beahrs Arnold Kremen Minneapolis		"Fertility and Infertility" John Sciarra Minneapolis
	"Preventing Complications of Acute Meningitis" M. R. Gomez Rochester		"Clotters and Bleeders" J. Roger Edson Paul R. Finley Minneapolis		"Abdominal Pain" Lyle J. Hay Minneapolis
	"Current Status of Organ Transplantation" J. S. Najarian Minneapolis		"Belchers and Bloaters" W. D. Blackwood M. D. Levitt Minneapolis		"Practical Management of Acute Head Injuries" R. F. Galbraith E. S. Wisiol Minneapolis
	"Hemorrhoids—To Operate or not to Operate, That May Be the Question" Clyde E. Culp Rochester		"Chest Injuries" Richard E. Larson Minneapolis John Culligan, St. Paul Josiah Fuller, Duluth		"Nonsuture Technique in Surgical Treatment of Varicose Veins" D. A. Felder St. Paul
	"Cutaneous Patterns of Fatal Disease" R. K. Winkelmann Rochester		"Reflux and the Assaulted Kidney" G. W. Koos Minneapolis		"Anesthesia in the Office and Emergency Room" J. W. Smith St. Cloud
	"Hand Injuries—13 Things to Avoid" Kenath H. Sponsel Minneapolis		"Menopause—An Organic vs. a Psychiatric Problem?" Bruce F. P. Williams Duluth		"The New Diuretics" D. A. Duncan Minneapolis
	"Thyroid Function Testing—An Exercise in Medical Detection" C. A. Gorman Rochester		"Rheumatism and Drugs" Paul Andreini Rochester		"Pulmonary Insufficiency" W. A. Corson R. V. Ebert Minneapolis
	"Burns—How to Treat Them" J. W. LaFave St. Paul		"The Threatening Eye" William Slack Duluth		"Saving the Cold and Pulseless Limb" Yoshio Sako Carl Manz Minneapolis
	"Multiple Injuries" John F. Perry, Jr. St. Paul		CCU ECG Group Problem Solving Sessions Gerald Lee, St. Paul		

During Intermission Visit Exhibits

Dermatology

Radiodermatitis

RADIODERMATITIS is an acute or chronic inflammatory disorder caused by the application of x-rays or radium. Cases are now rare. Care and precaution should govern the use of ionizing radiation on the skin. Its use in the treatment of benign dermatoses has decreased greatly within the past decade because of the development of antibiotics, steroids, etc. There has also been a tendency to use lower kilovoltage (60 kv). Approximately 300 to 400r administered to one square inch of skin will produce an erythema in seven to 10 days; larger doses invoke more intense reactions (acute radiodermatitis). Fractional treatment infers the application of small amounts (50 to 75r) at weekly intervals. In massive or intensive treatment the total dose is applied only once (e.g., 1500r sharply localized to a plantar wart). Divided dosage means that the total amount is split into several smaller fractions given daily, every other day, twice weekly, etc. For example, if a cutaneous carcinoma were to be treated with a total dose of 3000r, the individual doses might be divided into 6 of 500r each.



Figure—Chronic radiodermatitis. Patient had psoriasis and was treated excessively with fractional doses of x-rays.

Acute Type

First degree radiodermatitis consists of erythema with slight burning, itching, and scaling, which disappears after a few days or weeks. There may be temporary alopecia; pigmentation develops later.

Edema, intense erythema, and vesiculation typify second degree radiodermatitis, followed by exudation, erosion, and crusting. There is loss of hair which may be permanent. Sebaceous and sweat glands become less active. Atrophy and telangiectasia appear several months later.

Necrosis and ulceration characterize third degree radiodermatitis. Recovery may take several months; in some instances the ulcerations are so indolent that they never heal.

Chronic Type

This form may develop after the acute type or insidiously as a result of many fractional (suberythema) doses. The skin is dry, thin, smooth, shiny, and sensitive to trauma. Itching and burning are prominent symptoms. There is both hyper- and hypopigmentation and telangiectasia. The nails may be striated, discolored, brittle, or lost. As the disorder progresses multiple keratoses appear. Carcinoma develops in about 20% of the cases, usually squamous rather than basal cell in type. Sarcoma may arise in areas of radiodermatitis.

Mild radiodermatitis responds to measures used for corresponding phases of dermatitis due to other causes. Ointments or creams containing a steroid and an antibiotic are helpful in first degree radiodermatitis. If vesiculation is present, moist compresses of Burow's solution are effective. Severe cases, with necrosis and ulceration, require excision followed by grafting.

Carl W. Laymon, M.D.*
Minneapolis, Minnesota

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*From the Department of Dermatology, Hennepin County General Hospital, and the University of Minnesota Medical School, Minneapolis.

Reprint requests to 538 Southdale Medical Building, Minneapolis, Minnesota 55435.

From an 18th Century French Drug Dictionary

Ickey!

"All parts of man, his excrescences and excrements, contain oil and sal volatile, combined with phlegm and earth. Skull, brain, and calculus are employed in medicine, and are referred to in their proper places. Burning hair, smelt by patients, will counteract the vapors. Moss of the human skull, human blood, and human urine all have their uses in medicine. The saliva of a robust young man, taken fasting, is an antidote against the bites of serpents and mad dogs. Wax from the ears is good against whitlows. Nails from the fingers and toes, given internally either in substance or infused in wine, make a good emetic. Women's milk is pectoral, good in phthisis, and useful to apply to inflamed eyes. Fresh urine, two or three glasses drunk in the morning fasting, is good against gout, hysterical vapors, and obstructions. It may also be applied externally in gout and in skin complaints. Excrement of man can be applied to anthrax, plague bubos, and quinsies. Dried and powdered, it is recommended in epilepsy and intermittent fevers. Dose, one scruple to a drachm."*

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*Saul, F. William, M.D.: Pink Pills for Pale People, 1949.

Overweight

After a month on a new diet, Mrs. Jones was asked what she weighed. "One hundred and plenty," she replied.

Laboratory Letter

Three Lipid Tests

THREE LIPID TESTS—cholesterol, triglyceride, and lipoprotein electrophoresis—are now available in many laboratories. In this letter, I wish to speak to you about how you can use these tests to pin down what type of hyperlipoproteinemia your patient has.

Briefly, the facts on fats are these. At least five lipid disorders exist. Each has either a high cholesterol, a high triglyceride or elevations of both. And each carries its own symptoms, has its own outlook, and responds differently to diets or drugs. All, and here is this letter's gist, can usually be defined by three tests—cholesterol, triglyceride, and lipoprotein electrophoresis—and your knowledge of the patient's past and present state.

But how, you may ask, should I investigate patients in whom I suspect a lipid disorder? I would suggest you first order a cholesterol and triglyceride, especially if you spot a milky or turbid plasma from a fasting patient after it has been stored overnight at 4°C. If both tests are normal, your patient probably does not have a hyperlipoproteinemia. If either test is up, however, lipoprotein electrophoresis may help you define a specific type of hyperlipoproteinemia, as indicated by the list below.

					Food Sensitivity		
Type	Serum	Chol.	Trigly.	Lipid Electrophoresis	Fat	Carbohydrates	Clinical* Information
I	creamy	normal or high	high	chylomicron band; other lipoproteins down	yes	no	Rarest type; familial; occurs in children and causes bouts of abdominal pain and xanthomas; to treat, limit fats to 20% of calories.
II	clear	high	normal or high	beta-lipoprotein up	no	no	Most common type; patients may have xanthomas in tendons and xanthelasma and family history of coronaries before 50; tend to have premature infarcts; may be secondary to mxyedema, myeloma, macroglobulinemia, nephrosis, and liver disease; low cholesterol diets and lipid lowering drugs may help if condition detected early.

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*All patients except Type I will respond to some degree to diets low in cholesterol and high in unsaturated fats. Types with high triglycerides, III, IV, and V, may all present with mild diabetes, mild obesity, and early coronary artery disease. If these patients reduce, take in less than 50 grams of carbohydrate each day, and eliminate pure sucrose from their diet, their triglyceride levels (and usually their cholesterol values) will fall. For details on diets, consult: Levi, R. I., and Fredrickson, D. S.: Diagnosis and Management of Hyperlipoproteinemias, Amer J Cardiology, 22:576-586, 1968; and Wessler, S., and Avioli, L. A.: Classification and Management of Familial Hyperlipoproteinemia, JAMA, 207:929-933, 1969.

Type	Serum	Chol.	Trigly.	Lipid Electrophoresis	Food Sensitivity		Clinical Information
					Fat	Carbohydrates	
III	clear, cloudy, or milky	high	high	pre-beta and beta-lipoproteins up "broad beta disease"	no	yes	Uncommon; patients may have xanthomas in palms, arcus senilis, but often coronary disease first sign. Therapy consists of weight control and low fat, low cholesterol, isocaloric diet. Atromid-S and cholestyramine effective.
IV	clear, cloudy, or milky	high or normal	high	pre-beta lipoprotein up	no	yes	Fairly common in overweight patients with mild diabetes; men with this type may have infarcts before forty. Responds to weight reduction. Use sugar-restrictive low carbohydrate, low-calorie diet. Alcohol consumption also ought to be reduced.
V	turbid or milky	high	high	chylomicron band; pre-beta lipo-proteins up	yes	yes	May present as abdominal pain in late teens or may be secondary to insulin-dependent diabetes, pancreatitis, alcoholism or nephrosis, glycogen storage disease, myxedema and acute metabolic processes. Treat high-protein, low-calorie diet.

Richard L. Reece, M.D.
Minneapolis, Minnesota

It's the Law

Leaving Sponge in Body Not Necessarily Negligent

A physician removed a cancerous tumor from a patient's lung. A routine x-ray, taken the following day, disclosed a surgical sponge in the chest cavity. The operative procedure had been difficult, associated with the loss of eight units of blood. Nearly 100 sponges were used during the progress of the operative procedure. The usual safeguards concerning retained sponges were observed. In this case, the sponge count at the completion of the procedure was reported as correct. In addition, the operative note indicated that the chest cavity had been explored by the operating surgeon for evidence of retained sponges and none were found.

Several days later, the patient was returned to the operating room for removal of a sponge along with some clotted blood and old fibrin.

The jury found that the physician was not negligent under Minnesota law. The mere fact that the sponge was left within the thoracic cavity is not evidence of negligence. The patient was not awarded damages.

"No."—Miller v. Tongen, 161 N.W. 2d 686 (Minn., Sept. 27, 1968). The Citation, Vol. 18, No. 5 December 15, 1968.

Review

Factors Influencing Vitamin B_{12} Absorption

FACTORS OTHER THAN those in classical Addisonian pernicious anemia are known to influence absorption of vitamin B_{12}. This report is a review of some of the factors implicated in faulty absorption of that vitamin. The case report presents an example of impaired vitamin B_{12} absorption in a patient who did not have classical Addisonian pernicious anemia.

Case Report

History

A 59-year-old white, widowed male was admitted to Hennepin County General Hospital on August 14, 1968, for impending delirium tremens. A previous admission in November 1967 was for an alcoholic seizure disorder following a long history of heavy alcohol ingestion. He was diagnosed as having parenchymal cerebellar degeneration, probably secondary to alcohol.

Physical Examination: On the present admission the blood pressure was 120/70, pulse 100, respiratory rate 12, and temperature 98 degrees. The patient was thin, uncooperative, unkempt, but in no acute distress, and was fairly well oriented. Pertinent physical findings included arcus senilis, poor skin turgor, sinus tachycardia and an enlarged liver palpable two finger-breadths below the costal margin.

Laboratory Findings

The admission hemoglobin was 13.2 gm/100 ml; the white count was 8,700 with a normal differential. After hydration the hemoglobin was 10 gm percent, the hematocrit 30 percent, the platelet count 127,000/ml, and the reticulocyte count 0.6%. Cell indices revealed MCV 105, MCHC 31.3, and MCD 8.1. Bone marrow on August 29, 1968, showed erythroid hyperplasia with toxic neutrophil changes and decreased bone marrow iron stores; peripheral morphology revealed a normochromic, macrocytic anemia. The serum iron was 40 mcg%, IBC was 150 mcg% with 27% saturation. A Schilling test without intrinsic factor on September 6, 1968, showed 4.0% urinary excretion. The serum folate level was 2.2 $m\mu$/g/ml and the B_{12} level was 1,300 $\mu\mu$gm/ml.

Hospital Course

The patient was placed on folic acid 15 mg daily by mouth and ferrous sulfate 300 mg tid by mouth. A reticulocytosis of 4-5% occurred with hemoglobin remaining at 10 to 11 grams with reticulocyte counts of 3 to 4%. A second folate level three weeks after the first determination was 25.8 mgm/ml. A Schilling test done at this time (without intrinsic factor) showed a urinary excretion of 20.3%.

The reticulocytosis has continued and his hemoglobin has risen to 12.6 gm percent.

The results of the Schilling tests done on this patient suggest that the low initial vitamin B_{12} absorption was probably related to folate and/or iron deficiency, since the Schilling tests became normal after administration of folic acid and iron.

Classical Addisonian Pernicious Anemia

The clinical features of pernicious anemia were fully described by Addison in 1855; and the signs and symptoms of sore tongue, numbness, tingling and weakness, together with macrocytic anemia and achlorhydria form a well known clinical picture.[1] The response of this disease to parenteral vitamin B_{12} therapy implies a defect of absorption of this vitamin somewhere along the alimentary tract.

The gastrointestinal absorption of physiologic quantities of vitamin B_{12} may be divided into three phases:

1. Secretion by the gastric mucosa of a factor of unknown chemical structure designated intrinsic factor, to bind vitamin B_{12}.
2. Attachment of the intrinsic factor-vitamin B_{12} complex to the intestinal mucosa of the ileum by a calcium-dependent bond. The role of calcium is emphasized by lowered serum B_{12} levels and impaired absorption in man after the use of oral calcium-chelating agents.
3. The release of vitamin B_{12} at or within the intestinal mucosa by a substance with activity assumed to be enzymatic.[2]

Congenital Abnormalities of B_{12} Absorption and Utilization

Juvenile Congenital

Juvenile "congenital" pernicious anemia is characterized by vitamin B_{12} deficiency appearing in early life secondary to a congenital lack of intrinsic factor but with no other abnormalities of the stomach or its secretions.[3] This type responds to oral intrinsic factor supplementation, differentiating it from other causes of B_{12} deficiency in children. The diagnosis can be made by the following criteria: absence of gastric intrinsic factor activity; normal gastric mucosa histology; free hydrochloric acid in gastric juice; abnormal Schilling test; absence of serum antibody to intrinsic factor and parietal cells; correction of B_{12} absorption defect with intrinsic factor; no associated polyendochrinopathies (see below). The genetic basis for this disease has not been delineated.[3]

Familial Malabsorption

There are other types of pernicious anemia in children. Familial selective malabsorption of vitamin B_{12} is a rare, genetically determined disorder characterized by an isolated defect of vitamin B_{12} absorption and persistent proteinuria. Patients with this disorder also have free gastric acid, secrete adequate amounts of intrinsic factor and have a normal gastric mucosa. The mechanism responsible for failure to absorb B_{12} in the presence of intrinsic factor is obscure, although an intestinal defect has been postulated. Antibody activity against intrinsic factor remains a possible but unproven mechanism. Parenteral vitamin B_{12} therapy controls the disease. Approximately twenty-seven cases of this disorder have been documented.[4,5,6]

Endocrinopathies

There may be an association of pernicious anemia in children with endocrinopathies such as familial and idiopathic hypoparathyroidism and familial Addison's disease. It has been suggested that this condition is mucoviscidosis.[7,8]

Transitory intestinal malabsorption of vitamin B_{12} may coexist with congenital pernicious anemia in children as it does in adults. The diagnosis of congenital pernicious anemia is established by the criteria noted above. In these patients the normal absorption of B_{12} with intrinsic factor after therapy indicates that the selective malabsorption of B_{12} which was originally present was probably caused by B_{12} deficiency secondary to lack of intrinsic factor.[9]

A rare but well delineated genetic block in pyrimidine synthesis, transmitted as an autosomal recessive trait and clinically identifiable by the triad of infantile megaloblastic anemia, orotic aciduria and growth retardation has been documented. This anemia is refractory to vitamin B_{12} and folic acid. Oral administration of uridine bypasses the metabolic block and effectively alleviates the megaloblastosis, crystalluria and growth retardation.[10]

"Intestinal Steal Syndromes"

Under the term "intestinal steal syndromes," three general conditions related by a "competition" between the host and a parasite (or saprophyte) for available vitamin B_{12} are described. These include fish tapeworm infestation and anatomical variations in the intestinal tract due to natural disease processes, or occurring as the result of surgical procedures.

Fish Tapeworm Infestation

It is estimated that approximately twenty percent of the population of Finland is infested with the fish tapeworm *Diphyllobothrium latum (Dibothriocephalus latus)*, and a small percentage of these people manifest signs and symptoms of vitamin B_{12} deficiency. The mechanism whereby this worm utilizes or "steals" B_{12} has been studied; there are three principal means by which the worm might influence B_{12} uptake of the host:

1. It may destroy intrinsic factor or use it for its own B_{12} uptake.
2. It may split the B_{12}-intrinsic factor bond, prevent its formation, or use the entire complex.
3. It may inhibit the absorption process in the mucosa and/or the secretion of intrinsic factor.

The Schilling test with and without intrinsic factor was performed on worm carriers with and without anemia. After expulsion of the worm, another Schilling test was performed. In the worm carriers, increase in B_{12} excretion, when the test was performed with intrinsic factor, was only slight with the worm in situ. On the other hand, a significant increase in the Schilling values occurred after expulsion of the worm. This indicates that *D. latum* influences the B_{12} intrinsic-factor complex and/or has a blocking effect on the intestinal mucosa, resulting in inhibited B_{12} absorption.[11] Further studies using human gastric juice and hog intrinsic factor incubated with the worm, with and without added ^{60}Cobalt labeled B_{12}, indicated that the worm is capable of splitting the B_{12}-intrinsic-factor complex and also of impairing the B_{12} binding capacity of intrinsic factor.[12]

Intestinal Strictures, Fistulae and Diverticula

Megaloblastic changes in the marrow, response to vitamin B_{12} therapy and peripheral blood morphology similar to pernicious anemia have been described in cases of stricture in the lower ileum, strictures and ulceration of the jejunum, ileocolic fistula following tuberculous peritonitis, and in a variety of intestinal diverticula including those in the duodenum.[13,14] All of these patients respond to parenteral vitamin B_{12} therapy and recover spontaneously after corrective surgery. However, the mechanism involved is poorly understood. A decrease of absorptive surface does not appear to be involved in most cases, because absorption studies are usually normal. Bacterial "toxin" theories suggesting that bacteria in the diverticula or otherwise altered intestine produce some substance which inhibits absorption of B_{12} either by interfering with B_{12} or with mucosal cells remain unproven. In these cases abnormal small bowel flora may be presumed to be present (by other autopsy and dog studies). A pronounced increase of B_{12} absorption occurs with tetracycline administration, lending evidence to the concept that intestinal stasis causes bacterial overgrowth and direct bacterial interference with normal B_{12} utilization. Regional enteritis and sprue, not characterized by intestinal stasis, may demonstrate decreased B_{12} absorption which is not corrected with tetracycline.[15]

Blind Loop Syndrome

Certain surgical procedures performed on the gastrointestinal tract may leave a blind loop or be followed by intestinal stricture with subsequent development of macrocytosis and anemia which seems almost always to be due to B_{12} deficiency. The mechanism of defective B_{12} absorption involved in such blind-loop syndromes or iatrogenic strictures, etc., appears to be due to the presence of an abnormal intestinal flora, as in the case of strictures and diverticula, and, like these, is corrected by tetracycline administration.[13]

The Effect of Subtotal Gastrectomy

It is interesting to note that in a large study of 292 patients with a 60% gastric resection and Billroth I or Polya type reanastomosis for benign ulcer, anemia resulted in 53 percent of the cases (hemoglobin levels less than 13.6 gm/100 ml in males and less than 11.6 gm percent in females). Iron deficiency was noted in 44 percent of these patients and was unassociated with other causes of anemia in 55 of the 292 patients. There was associated morphologic evidence of B_{12} and/or folate deficiency in 84 of the 292 patients. B_{12} deficiency was diagnosed in 20 percent (B_{12} levels less than 160 $\mu\mu$gm/ml and morphologic evidence). The incidence of this deficiency increased, becoming maximum six to eight years after surgery. Folate deficiency occurred in twenty-six patients (serum folate less than 6 mμg/ml and morphologic evidence), but there was no correlation between the time of surgery and the time the folate deficiency was diagnosed. The mechanisms of anemia are probably chronic subacute gastrointestinal hemorrhage and reduced iron absorption plus deficiency of gastric intrinsic factor in the first two types; the mechanism of the folate deficiency is not understood.[16]

Malabsorption Syndromes Resulting in Abnormal B_{12} Absorption

The common denominator of nontropical sprue, tropical sprue, celiac disease and idiopathic steatorrhea is impaired intestinal absorption of various dietary substances. The etiology of these syndromes remains obscure but all may be included in the term "malabsorption syndrome." Secondary forms of malabsorption such as bowel resection, the "blind-loop syndrome," lymphosarcomas and intestinal lipodystrophy show gross pathological changes.

Schilling tests reveal decreased vitamin B_{12} absorption in both primary and secondary types which is not improved when done with intrinsic factor.[17]

Neomycin has been implicated in a malabsorption syndrome very similar to nontropical sprue. Patients studied with this condition show a decrease of 20-60% in Schilling test urinary excretion values, but these do not reach the low levels of absorption of pernicious anemia or more serious malabsorption syndromes.

Generally speaking, Addisonian pernicious anemia can be separated from megaloblastic anemias due to malabsorption by doing the Schilling test with and without intrinsic factor, addition of intrinsic factor failing to correct inadequate B_{12} absorption in the malabsorption syndromes, whereas absorption is normal in pernicious anemia when intrinsic factor is given.

It is important to be sure of the quality of the intrinsic factor used when doing Schilling tests in such studies. Intrinsic factor preparations of poor quality have been known to affect the results of the test when they are performed using intrinsic factor.

Faulty B_{12} Absorption Secondary to Deficiencies

Vitamin B_{12} Deficiency

Vitamin B_{12} deficiency due to intestinal malabsorption may result in gastric atrophy and loss of intrinsic factor formation. In such cases, if the damage has not progressed too far, reversal of gastric damage and return of intrinsic factor secretion may result from vitamin replacement therapy. Evidence suggests that secondary intestinal malabsorption of B_{12} is not rare in pernicious anemia and results from deficiency of the vitamin. A vicious cycle is thus set up.[18] This was demonstrated in a Hindu immigrant to this country who ate no meat. B_{12} absorption was shown to be defective by the Schilling test and failure to respond to oral B_{12}. The gastric juice contained abundant intrinsic factor at a time when he could not absorb B_{12}. With parenteral B_{12} therapy, the defective absorption of vitamin B_{12} disappeared. This "vegans syndrome" demonstrates the vicious cycle; absence of B_{12} damages the mucosa to the point where it fails to absorb B_{12}, at which time dietary B_{12} intake is of no value.[19]

Folate Deficiency

The effect of folate on B_{12} absorption has long been debated. Studies on patients with megaloblastic anemia of pregnancy show low serum folate levels in 83 percent (also decreased in 26 percent of nonanemic patients in their ninth month). Assays of vitamin B_{12} were decreased in 71 percent of anemic patients and in 46 percent of nonanemic patients in the ninth month of pregnancy.[20,21] Patients have been described with megaloblastic anemia associated with low serum folate levels and normal or borderline low serum B_{12} levels, but the Schilling test values proved that these patients did not have pernicious anemia. After treatment with folic acid the B_{12} values spontaneously returned to normal, thereby ruling out pernicious anemia. Perhaps folic acid is directly involved in B_{12} absorption, a number of folate-deficient patients having shown abnormal Schilling tests with and without intrinsic factor. Two such patients had normal B_{12} absorption following treatment with folic acid.[22] As is well known, folic acid therapy will temporarily correct the defect in nucleoprotein metabolism in pernicious anemia, but relapse eventually occurs unless B_{12} therapy is instituted.[23]

Iron Deficiency

Patients with iron-deficient normocytic anemia occasionally have associated vitamin B_{12} deficiency. In thirteen patients with this condition treated solely with iron, serum B_{12} levels spontaneously returned to normal within ten weeks. The suggested explanation is that B_{12} levels were restored when B_{12} absorption was corrected by iron therapy. It was also noted that ten of these thirteen patients with B_{12} deficiency had no free acid in the gastric contents after histamine stimulation. Such patients could be examples of incipient pernicious anemia. However, if the B_{12} deficiency in these patients were due to increased intrinsic factor secondary to chronic atrophic gastritis, then this decrease must be reversible, since the serum B_{12} levels increased after iron therapy, which they do not do in pernicious anemia.[24]

Vitamin C Deficiency

Vitamin C deficiency may be related to

megaloblastic anemia. If plasma levels of vitamin C are decreased and if ascorbic acid is given, reticulocytosis and improvement in the anemia may occur. This alteration in ascorbic acid metabolism may reflect changes in redox potentials associated with B_{12} deficiency. Vitamin C also plays a prominent role in maintaining the folic acid coenzymes in the reduced or active state, thus influencing folate metabolism and thereby perhaps influencing B_{12} absorption.[23,25]

Protein Malnutrition

Studies on rhesus monkeys made hypoalbuminemic to stimulate low protein states showed markedly decreased absorption of ^{58}Cobalt-labeled B_{12} which was completely corrected with protein repletion. This suggests damage to the intestinal mucosa and perhaps a decrease in intrinsic factor production from protein depletion which may be responsible for the decreased vitamin absorption.[26]

Effect of Drugs on B_{12} Absorption

Anticonvulsant Drugs

Some patients develop megaloblastic anemia while on anticonvulsant drugs. The majority of these cases respond to folate therapy, but occasional patients respond to B_{12} alone. Evidence of some disturbance in folate metabolism can be detected in the majority of epileptics treated with anticonvulsants. It is suggested that a functional change occurs in the intestinal wall in some patients taking anticonvulsant drugs and that this change may result in a relative defect in B_{12} absorption sufficient to produce a deficiency. Drugs implicated include Primidone, barbiturates, Phenytoin, phenobarbitone, dilantin, and Mysoline.[27,25,28]

Paraaminosalicylic Acid

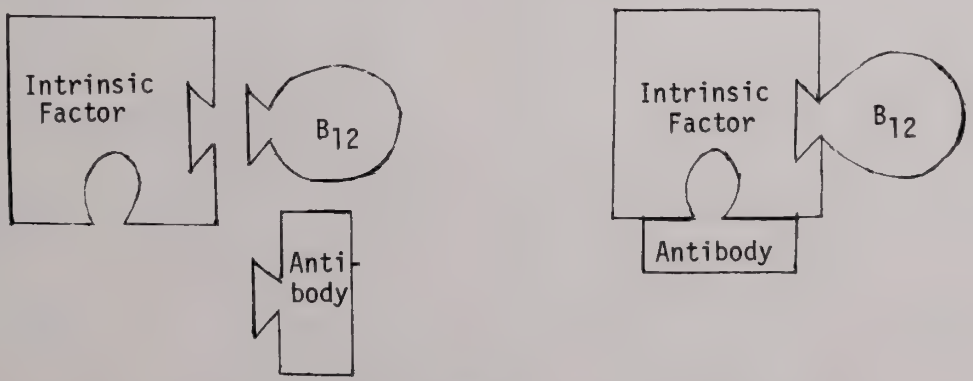
Patients taking paraaminosalicylic acid who do not have pernicious anemia may have abnormal Schilling tests which do not correct with intrinsic factor. Schilling test values after discontinuing the paraaminosalicylic acid, even without intrinsic factor, were normal. The excretion values of B_{12} in patients on paraaminosalicylic acid are diminished five to seven times. The mechanism is thought to be due to a malabsorption of B_{12} in the small intestine.[29]

Colchicine

Orally administered colchicine may affect vitamin B_{12} absorption. Studies show that this inhibition of absorption is greatest when the colchicine is directly instilled into the ileum, suggesting an induced defect of the ileal mucosa which is reversed when the drug is discontinued.[30]

Immunologic Factors in Vitamin B_{12} Malabsorption

More than 50 percent of all patients with adult type Addisonian pernicious anemia have circulating antibody to intrinsic factor, measurable either as antibody which blocks the ability of B_{12} to attach to intrinsic factor (blocking antibody), or as an antibody which combines with intrinsic factor in such a manner as to allow precipitation of the complex (precipitable antibody), or both.[31]



Figure

Blocking antibody-blocks B_{12} binding to intrinsic factor.

Precipitating antibody-binds to free intrinsic factor and also to intrinsic factor-B_{12} complex.[32]

About ninety percent of patients tested have antibodies to parietal cells, and about fifty percent have antibodies directed against the thyroid gland. The high incidence of antibodies in patients with pernicious anemia in combination with histologic features of chronic inflammation and atrophic gastritis suggests an autoimmune factor. This is partly substantiated by the high incidence of thyroiditis and myxedema in patients with pernicious anemia. However, these antibodies have not yet been shown to be harmful to gastric mucosa. The precipitating antibody has been demonstrated in the saliva of a patient with pernicious anemia and identified as an IgA immunoglobulin.[33,34] In a series of eighteen patients treated with prednisone, seven showed an increase in intrinsic factor production sufficient for normal B_{12} absorption. After steroid therapy normal gastric glands containing parietal cells were seen in atrophic mucosa in nine of the eighteen patients. The effect of steroids on gastric function and structure was in part found independent of the effects of gastric antibodies and may be a secondary phenomenon.[35]

Summary

A variety of conditions are discussed which result in decreased absorption of vitamin B_{12}. Included are classical Addisonian pernicious anemia, congenital defects of vitamin B_{12} absorption, parasitic conditions, malabsorption syndromes, deficiency states, drug interactions, and immunologic aspects related to B_{12} absorption. A patient is presented who demonstrates a defect in vitamin B_{12} absorption corrected with oral administration of folic acid and iron.

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Note: I am indebted to Dr. Robert A. Green for his constructive review of this manuscript, and to Mrs. Lorraine Seaverson for kindly typing the manuscript.

This study was done during a medical elective in oncology-hematology at Hennepin County General Hospital.

*Senior Medical Student, University of Minnesota Medical School.

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The G. P.

A country doctor needs more brains to do his work passably than the fifty greatest industrialists in the world require.—Walter Pitkin

Book Reviews

Books are men of higher stature, and the only men that speak aloud for future times to hear.—E. B. Browning

1967-68 COLLECTED PAPERS IN MEDICINE AND SURGERY FROM THE MAYO CLINIC AND THE MAYO FOUNDATION. Volume 59. Two volumes $46.00. Singly $25.00. 511 and 578 pages. W. B. Saunders, Philadelphia, 1968.

This distillation of the awesome collection of papers published in one 12-month period by the Mayo Clinic staff will provide the reader with hours of instruction in many fields of medicine and surgery. The tab is high, but some papers alone are worth the price of the two volumes. For instance, McGoon's Olympian and total survey of cardiac surgery, condensing into one article the two that appeared last year in the New England Journal of Medicine, must be required reading for all cardiologists, though this reviewer cannot accept all of McGoon's "A" ratings for cardiac surgical conditions.

With this high praise McGoon will forgive an editorial correction: two ductuses do not make a couple of ducti. "Fibromuscular dysplasia and other uncommon diseases of the cervical carotid artery: angiographic aspects," by Houser and Baker is based upon more than 5000 cerebral angiograms and concerns 28 cases of non-atheromatous irregularities. Of these, 16 were fibromuscular dysplasia. The authors call attention to iatrogenic carotid artery disease following angiography. No therapy is discussed.

Aside from libraries, the natural audience for and purchasers of these volumes are the alumni of Mayo fellows. The books do offer a ready answer to most questions, such as: "How did the Mayo Clinic do it back in 67-68?"

R. Berman, M.D.
Minneapolis, Minnesota

BRAY'S CLINICAL LABORATORY METHODS, revised seventh edition by John D. Bauer, M.D., Philip G. Ackerman, Ph.D., and Gelson Toro, Ph.D. The C. V. Mosby Company, St. Louis, Missouri, 1968. Color plates 16. Pages 721. Appendix pages 3. Price $14.85.

The revised seventh edition is practically a new book. Drs. Bauer, Ackerman and Toro have updated the text, added new illustrations, and arranged the subjects in a logical order. Yet there are deficiencies. Iron metabolism, for instance, is too briefly discussed, and no mention is made of the iron-ascorbic acid chelation mechanism. The immunologic aspects of pernicious anemia are not discussed. The color plate "3" of the Friedman test is superfluous since this test has been replaced by more sensitive laboratory methods.

Though the term "pyknocyte" applied to the erythcocytes shown in Figure 4-15 may be acceptable, the cells presented in Figure 4-19 are not true "poikilocytes" but are examples of drying and staining artefacts. While the pathologic erythrocyte shown in Figure 4-22 is interesting, the concept however, that atypical or incomplete nuclear disappearance may leave a remnant of the nuclear membrane, forming a Cabot ring, is not valid (page 133).

The chapter on "Blood groups, blood typing and crossmatching" is one of the best presentations of these subjects I have encountered in clinical laboratory books. The chapters on clinical chemistry, serology, virology, parasitology, mycology and toxicology are well done.

Though the book has shortcomings they do not outweigh the many good features of the work. It is thus recommended to residents in clinical pathology, medical students, and medical technologists.

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Minneapolis, Minnesota

ATLAS OF EAR SURGERY, William H. Saunders, M.D. and Michael M. Paparella, M.D., Editors: C. V. Mosby Company, 1968; 363 pages. Price: $27.50.

This is a timely publication containing up-to-date information, which fills a gap in the library of the otolaryngologist. Operative procedures on otosclerotic deafness, fenestration, stapedectomy), reconstructive middle ear and mastoid surgery (tympanoplasty) are fully covered in detail.

The authors have also included all the essential operations in tumors, cosmetic, and reconstructive surgery of the ear. A section is devoted to the facial nerve surgery, and also the surgical treatment of Meniere's disease.

The print is of first quality; the illustrations are clear and artistic. The authors have magnificently accomplished a description of the operations precisely, briefly, step by step, with a special emphasis on the surgical technique.

They should be congratulated for this fine contribution. It is a reading must for every graduate student in otolaryngology and maxillo-facial surgery.

Ekrem Gozum, M.D.
Minneapolis, Minnesota

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Methamphetamine HCl	1.0 mg.	1.0 mg.
Cyanocobalamin	2.5 mcg.	1.5 mcg.
Intrinsic factor concentrate	8.0 mg.	–
Thiamine HCl	–	5.0 mg.
Thiamine mononitrate	10.0 mg.	–
Riboflavin	5.0 mg.	–
Niacinamide	50.0 mg.	–
Pyridoxine HCl	3.0 mg.	–
Calcium pantothenate	20.0 mg.	–
Ferrous sulfate exsic.	30.0 mg.	–
Ascorbic acid	100.0 mg.	–
		Contains 15% alcohol† † Some Loss Unavoidable.

Contraindication: Carcinoma of the prostate, due to methyltestosterone component.

Warning: Some patients with pernicious anemia may not respond to treatment with the Tablets or Capsules, nor is cessation of response predictable. Periodic examinations and laboratory studies of pernicious anemia patients are essential and recommended.

Side Effects: In addition to withdrawal bleeding, breast tenderness or hirsutism may occur.

Suggested Dosages: *Male and female*—1 Tablet or Capsule, or 3 teaspoonfuls Liquid, daily or as required.

In the female: To avoid continuous stimulation of breast and uterus, cyclic therapy is recommended (3 week regimen with 1 week rest period—Withdrawal bleeding may occur during this 1 week rest period).
In the male: A careful check should be made on the status of the prostate gland when therapy is given for protracted intervals.

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Computer Medicine

Basic Concepts in Computer Science for Laboratory Physicians*

THE DIGITAL COMPUTER may have more impact on hospital services in the next decade than any other scientific instrument. Hospital administrators are now aware of the advantages of using digital computers for cost accounting, communication, and inventory control; but until now, physicians have not come into contact with the digital computer.

Uses of Computers in Hospitals

Nevertheless, digital computers have some applications in the hospital setting. Today, computerized patient records, pharmacy systems, outpatient appointment systems, and clinical and research laboratory systems are being developed in many institutions. The purpose of this paper is to acquaint the hospital or laboratory physician with certain basic concepts that are fundamental to understanding and applying the digital computer to hospital work.

General Purpose Computers

Presently, over one hundred different general-purpose digital computers flood the market, their purchase price ranging from $6,000 to over $10,000,000. Every year use of the computer increases; it is becoming part of our everyday existence. The tasks these computers can perform are too numerous to mention; but the three fundamental types of application are business data processing, general scientific computing, and real-time, on-line control.

Computer Hardware Organization

The operational hardware system of the digital computer consists of a central processing unit and certain peripheral devices. Regardless of their application, all general purpose digital computer systems are similarly organized (Figure).

I am sure you realize that the design of these five basic sections varies from one machine to another. These differences in design enable certain computers to perform specific applications better than other computers and also contribute to their differential in price. Before we proceed, let's spend a few moments describing in greater detail the five basic sections of a computer.

Input Operation

When a computer analyst is describing an input operation, he is usually referring to data coming from an external device. Card readers, magnetic tape units or, in the case of laboratory, an on-line auto-analyzer may bring in this data. Typically, input data is transferred to the computer's memory via a temporary input/output register and the computer's accumulator. This transfer operation takes place under the guidance of the computer's control unit.

Control Unit

The control unit is the logical complex that determines what operation is performed and when; it has built into it certain logical operations that it can perform. The computer is capable of performing only those operations previously built into it. The instruction repertoire is a list of commands which can be used to make up a program for the computer. On our basic block diagram, the data from an external device can be stored under program control by using the computer's store command. This data will be placed in the computer's memory until it is needed for processing.

---

*This paper was presented at the Symposium of the use of the Digital Computer in the hospital laboratory sponsored by the Minnesota Society of Clinical Pathologists at the Minnesota State Medical Association, Annual Meeting in Rochester, Minnesota on May 13, 1968.

Memory

Memory is the principal element of the computer. The cost and speed of its memory largely govern the cost and speed of the computer. The memory stores the program to be executed; it also stores input data until it is needed for processing, intermediate results during computation, and final results until they are needed for output. The memory stores its contents typically in the form of words. The word generally consists of from one to six characters depending upon the computer.

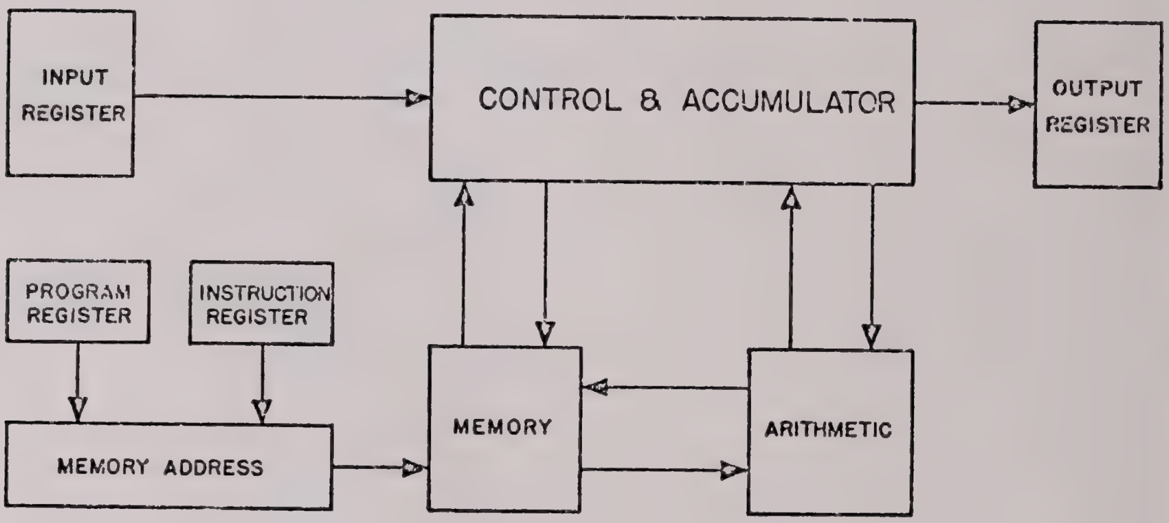
Word Size

When various manufacturers describe their products they typically refer to word size. This is the number of bits in a memory location. If six bits are necessary to represent a character, then a 12-bit machine would have the capability of representing two characters per word.

Memory Size

Another term frequently quoted by manufacturers is memory size. This is usually represented by two numbers, the smaller of which

Organization of a Digital Computer



Our basic block diagram consists of five basic sections of operation:

(1) input

(2) control

(3) memory

(4) arithmetic

(5) output

Figure

represents the number of words of storage provided by the manufacturer in the basic system, and the larger number representing the maximum expanded size of the computer. Thus, a machine specified as 4K expandable to 32K, has 4096 words of memory provided in the basic system which may be expanded to 32,768 words.

Cycle Time

Another term associated with the memory is cycle time, the time required to fetch a word from memory and then write it back. Typical third generation computers operate in the range from 700 nanoseconds through two microseconds.

Direct Memory Access

Many computers on the market today offer an option called direct memory access. This feature, referred to as DMA, allows an input/output peripheral device to put data directly into or take data directly from core memory. This type of option facilitates high speed data transfers and relieves the computer's control unit to perform other tasks.

Arithmetic Unit

The basic block diagram indicates a section labeled "Arithmetic Unit," which performs a specified arithmetic operation between a word contained in the computer's accumulator and the word fetched from memory. This section also contains the digital logic which has been prewired into the computer. On command, it will take two numbers and manipulate them according to instruction. It sometimes multiplies by successive adding and sometimes subtracts by complementing and then adding, always performing its specialized functions under the guidance of the computer's control section.

TABLE I
Peripheral Equipment

- I/O Typewriter
- Punched Paper Tape
- Punched Cards
- Digital Magnetic Tape
- Rotating Mass Memories
- Line Printer
- Special Analog/Digital Equipment
- Incremental Plotters
- Communications Equipment
- CRT Display Units
- OCR (Optical Character Readers)

Output

The final section on our basic block diagram is the output section, structured in similar fashion to the input section and allowing us to obtain the calculated results that have been performed on the input data. A variety of external devices may be connected to the input and output sections of the central processor. These external devices are referred to as peripheral equipment and operate at a much slower speed than the central processor unit. The peripheral devices, together with the central processor, compose an operational hardware system. The choice of peripheral devices that are used on a system depends upon the operational task to be performed. Examples of common types of peripheral devices appear in Table 1.

Peripheral Equipment

Typewriters

The I/0 typewriter is an input/output device which operates as a normal typewriter with the additional feature that the information typed from the keyboard is entered into the computer. The computer is also able to send output data to the typewriter which will automatically print it. This is a low-speed device, the rate at which data can be put in depending on the typing speed of the individual. This conversation device is used to make minor programming changes or to initiate certain programs. When large quantities of data are involved, it is usually more efficient and economical to transfer this information via punched cards, paper tape or magnetic tape, as the system can absorb these at its own rapid rate.

Tape

Punched tape is used extensively as an input medium in general purpose digital computers and in some business data processors. Punched tape equipment typically has a cost and speed advantage over card equipment; however, its format is not quite as flexible as card equipment.

Punched Cards

Punched card equipment is used to read or punch information onto a 3¼ × 7⅜ card commonly referred to as an IBM card. Card equipment is used extensively in data processing type applications and offers the degree of flexibility necessary in this field.

Magnetic Tape

Digital magnetic tape has become the traditional mass storage medium of many data electronic data processors. Data transfer rate is a major criterion for magnetic tape users. With high speed equipment, data transfer rates of up to 120,000 characters per second may be achieved. This device is a good medium for putting in large blocks of data or storing large volumes of historical or audit trail information. However, the access time, or the time required to find one specific piece of information on the magnetic tape, can vary from over 10 seconds to one thousandth of a second, depending upon where the specific piece of information is stored on 2400 foot rolls of tape.

Rotating Mass Memories

Rotating mass memories are devices that have a thin magnetic coding applied to a drum or disk. This unit is rotated past magnetic heads that are used to read or write on the surface. By this technique, access time in the order of milliseconds can be achieved. This random access type of device is typically used in real-time systems where there is normally a need for storing a large amount of data with the ability to retrieve specific items at a rapid rate.

In a clinical laboratory system, a disk or a drum would be used to store the patient file, which could be updated at a high rate as input results are obtained from the laboratory. Rotating memories are sub-divided into disks or drums and are further divided according to whether the device has a fixed head or a movable mechanical positioning of the heads. The mechanical characteristics of this medium affect the access time and also the flexibility of the device.

Line Printer

The line printer is an output device used to print rapidly large volumes of data. Printers that are available today will print 132 column lines at a rate of from 150 lines to over 1200 lines per minute. Special Analog/Digital equipment, communications equipment, and CRT display units are also available as peripheral equipment.

Software Building Blocks

We shall begin our discussion of software by examining some of the basic building blocks used by the programmer in putting together a system program (Table 2).

TABLE 2
Software Building Blocks

1. Machine Language Coding
2. Assembly Language
3. Procedure-Oriented Languages
    COBOL
    FORTRAN
    PL/I
4. Utility Routines
5. Operating Systems

Machine Language Coding

Most basic of these blocks is machine language coding. While all internal operations of a computer are initiated by machine-recognizable instructions, it is rare to write a program in machine language. The chief use of actual machine language coding is in debugging when a programmer inserts a small routine directly into the machine to patch his program. This can be useful on certain computers and is a valuable tool to an experienced programmer. However, even this practice is being replaced by symbolic, debugging software.

Assembly Language

Probably the most widely used software language today is assembly language, in which a programmer has access to all machine facilities and yet is relieved of most of the clerical tasks. The programmer writes instructions in a symbolic form which has more significance to him than a string of numbers.

Many assembly languages extend the power of the programmer by providing more sophisticated features, such as the macro instruction which is coded by the programmer very much like any other imperative statement. Its purpose is not to generate a single machine language instruction but to perform a higher level task which takes several instructions. Both machine language coding and assembly language programming are languages which require the programmer to be knowledgable in the characteristics of the computer. We shall now talk about some higher level languages which are procedure-oriented and do not require such an intimate knowledge of the computer hardware.

Procedure-Oriented Language

The first of these, COBOL, which stands for Common Business Oriented Language, is a major procedure-oriented language developed for business applications. It has evolved through the efforts of computer manufacturers, the Department of Defense and other organizations, and is designed to be a machine-independent language: that is, its syntax and vocabulary are not dependent upon pecularities of any particular computer but reflect the logic commonly encountered in business data processing.

Because of its English-like appearance, COBOL is self-documenting to a greater extent than machine-oriented programs. A major criticism of COBOL is that it does not use the hardware as efficiently as an experienced programmer who uses an assembly language. More storage is used and running time is longer. In the past, these objections were valid but are now being remedied to some extent as new compilers are written with the experience of past errors in mind.

Formula Translation

Fortran, an abbreviation of *FORmula TRANslation,* is a procedure-oriented language developed for use in scientific problem-solving and at this time is the most widely used procedure-oriented language. It is largely machine-independent; but because of the lack of standardization in its early development some adjustments are necessary to move from one computer to another.

PL/1

PL/1 is a new language designed for use on both data processing and scientific problems as well as for real-time and systems programming. It incorporates features found to be useful in previous languages such as COBOL and FORTRAN and takes into account new hardware features, such as mass storage and data communications.

Table 3 illustrates the instructing sequences required for coding the solution of an equation using machine language, assembly language, and FORTRAN.

There are other procedure-oriented languages, each with its own characteristics. Most of these languages have been developed for special applications. Therefore we will omit them here.

Utility Routines

Most software systems include programs that perform miscellaneous day-to-day functions. Some of these programs offer only minor conveniences while others are essential to daily operations. These routines are sometimes referred to as utility or service routines. Commonly used utility routines are generated to sort and to merge programs.

TABLE 3

Language Comparison

The following instruction sequences represent the coding for the solution of the general equation

$$G = A + B\,(C-D) + E/F$$

first in machine language, then assembly language and finally in higher level language (FORTRAN).

I. Machine Language

```
8005
3006
7007
8003
8004
5002
A001
A007
7007
```

II. Assembly Language

```
LDW E    Divide E by F
DVI F
STW G    Save Intermediate Result
LDW C
SUB D    Form C-D
MPY B    Multiply By B
ADD A    Add A
ADD G    Add E/F
STW G    Save Result in G
```

III. Higher Level Language (FORTRAN)

```
G = A + B * (C-D) + E/F
```

Another form of utility routine is the linkage editor which combines several segments into one routine and permits the repeated use of subroutines.

The most frequently used utility programs are the type which facilitate routine data handling. These include inquiries to auxiliary storage devices, tape copying and editing, and media conversions such as card to tape, tape to card, tape to print, etc.

Operating Systems

To the user of a data processing system, a measure of performance is the internal operating speed of a machine. This feature tells the user how fast a particular job can be processed once a run is started, but it does not take into account such variables as set-up time and delays while awaiting operating instructions. As machine speeds have increased, such overhead operations have taken on an increasingly important segment of time. To counteract degradation of system performance by manual intervention, operating systems have come into wider use, the general purpose of which is to automate manual procedures and at the same time provide a standard and helpful machine environment.

Most operating systems have three major tasks: language translation, job control and data control. Operating systems can accept properly identified programs in several languages and call on the proper translator to reduce the statement to some form of machine language.

Some advanced operating systems include multi-program features which provide significant time-saving advantages. With this capability two or more tasks can be processed concurrently.

A good operating system can be an effective means of multiplying programmer productivity, standardizing machine operations, increasing system throughput, and reducing the chances of undetected errors. A price must be paid for these advantages, however, because operating systems occupy storage space. In the case of advanced system, the storage used can be sizeable. Frequently a larger machine will be needed to accommodate the operating system. These alternatives present trade-off decisions which must be made by the prospective user.

Summary

The digital computer may be used in the hospital setting in three fundamental areas of application: business data processing, general scientific computing, and real-time, on-line control. We have summarized the five basic sections of operation in the organization of computer hardware. Basic definitions of input, control, memory, arithmetic and output have been presented. Various types of peripheral devices and equipment available to expand the capability of the central processing unit are outlined.

In our discussion of computer system software we have taken a brief look at some of the major building blocks available for software systems. We have looked at assembly language, and the various higher level languages or compilers. We have also examined some of the features of operating systems and utility programs. Proper selection of these and other building blocks is essential to the successful computer solution to everyday problems. Each application must be investigated on its own merit to insure that the correct techniques are used for that particular situation.

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Robert L. Strom, M.D.†
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Jumping to Conclusions

Mrs. White was taken suddenly ill in the night, and the new doctor was called because he was the nearest available.

After a look at the patient, the doctor stepped outside the sickroom to ask Mr. White for a corkscrew. Given the tool, he disappeared, but several minutes later was back, demanding a pair of pliers.

Again he disappeared into the room of the moaning patient, only to call out again, "A chisel and a mallet, quickly."

White could stand it no longer: "What ails her, Doc, for gosh sakes?"

"Don't know yet," was the reply. "Can't get my instrument bag open."

Diversified Numeric Applications On-Line Clinical Laboratory System

MODERN HOSPITAL clinical laboratories do an ever increasing number of chemical tests. With the advent of intensive care units and other specialized treatment areas, a need will develop for continuous chemical and electrical monitoring. Many instruments in today's laboratory are automated and produce so many results that they tend to overwhelm the physician. The answer to this plight is two-fold. First, a laboratory must produce a written document so that the physician can recognize abnormal quantitative trends; second, laboratory information must be delivered promptly to the patient's bedside and the physician's hands. The on-line digital computer offers satisfactory solutions to these problems.

Changes in Computers

The computer industry has undergone revolutionary changes over the past few years. These have particular significance to physicians. Newer, faster, more powerful computers have recently become available, at a fraction of previous costs. Because of the use of solid state, integrated circuit logic and new production techniques, manufacturers can reduce costs. As a result, for each dollar spent the computer user receives more computing power per dollar than he would have had a few years ago. Now, a clinical laboratory in a community hospital with 300 beds or more can have its own data processing system designed to fit its needs. This paper describes a low cost data processing system designed specifically for the hospital clinical laboratory.

Basic Design Criteria

The following basic design criteria were considered important if this system was to help the typical working clinical laboratory and not be merely an expensive experiment.

1. Laboratory personnel must be able to operate the system. It should require no skilled operators or programmers.
2. The system must function as a working tool of the laboratory technologist—much like any other instrument used in the laboratory. The system should not appear to be remote and mysterious.
3. The system must be such that technologists have no direct contact with the basic computer. They should work with peripheral devices so designed as to fit in with existing procedures.
4. The system must be inexpensive. The increased productivity and improved quality of laboratory work must justify the cost.
5. The system must blend with existing routines and not require any major changes in laboratory procedures.
6. The system must be simple and foolproof to use and convenient enough so that laboratory technologists readily accept it.
7. The system must, wherever possible, use the special abilities of the computer to improve the quality of laboratory work beyond that practical with manual techniques.
8. The system must operate 24 hours a day, seven days a week, for extended periods of time.
9. The system should have a 100% reliable backup procedure to handle the situation when part of the system fails.

On-Line Computer Capability

The above criteria can be met only with an on-line computer system, for, with such a system, the technologist can interact continuously with the computer much as he does with any instruments.

Though any computer system can detect human errors by analyzing the input data, only an on-line system can instantaneously notify

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*This paper was presented at the symposium on the use of the digital computer in the hospital laboratory sponsored by the Minnesota Society of Clinical Pathologists at the Minnesota State Medical Association Annual Meeting in Rochester, Minnesota on May 13, 1968.

the responsible individual, so that corrective action can be taken immediately, thereby minimizing the entry of erroneous data into final test reports.

Figure 1 illustrates how the laboratory system is organized and how it relates to all laboratory sections. Included are a small low-cost general purpose digital computer; auxiliary random access mass memory; several terminals located throughout the laboratories; analog to digital interface equipment; and one or more printing devices. The computer or central processor, together with its random access auxiliary memory, performs all of the decision making, data processing, and information storage functions of the laboratory system.

Central computer and auxiliary memory are placed in an out of the way location and are never touched during normal operation. Terminal devices control the system through a simple pushbutton operation.

The on-line clinical laboratory system handles laboratory data for inpatients, outpatients and emergency patients. It also collects and organizes the billing data for the hospital administration.

The Diversified Numeric Applications system can serve all sections of the laboratory, including chemistry, hematology, bacteriology and urinalysis. All system functions are on-line and are always available for instantaneous execution. The system has built-in provision for communication with other hospital computers, and can be utilized to output reports to critical areas such as emergency rooms, outpatient clinics, or other associated hospitals.

Description of the System

The best way to explain how a system operates is to review the procedures involved in a typical day's use. The sequence of events described are those that take place in a typical hospital. Differences exist between hospitals but the system is flexible enough to be modified.

The Laboratory Request Entry Console

Usually laboratory personnel collect routine requests during the night and in the morning for the day's run. Early in the morning, the accumulated requests are entered into the computer system. This may be done in several

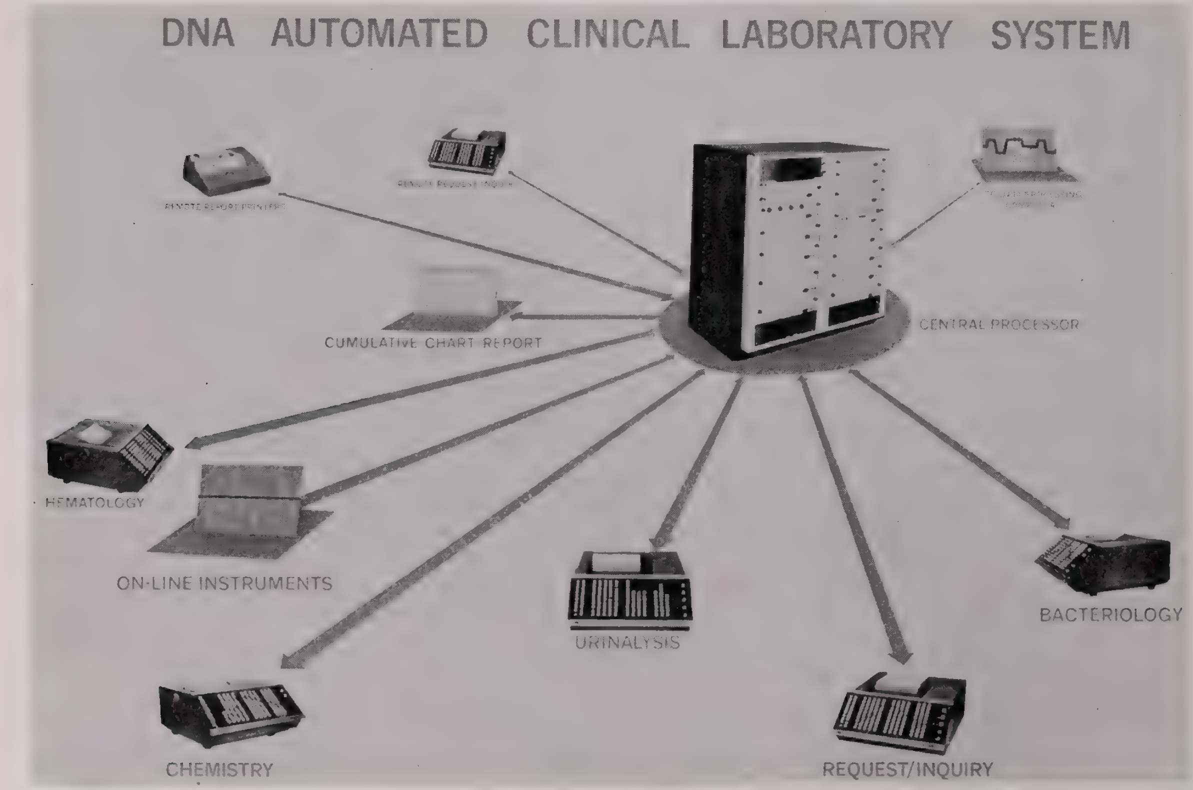


Fig. 1—Block Diagram

ways. The general case would be the one in which requests are brought to the laboratory on small request slips. Results are then entered into the computer through the Laboratory Request Entry Console (Figures 2 & 3).

Entering the Data

The procedure is to enter the patient number, ward or room number, plus a code number that corresponds to the particular tests requested. Miscellaneous codes are available to handle special cases like "No Charge." As the request data is entered, it is stored in the console to be verified. No data is transmitted to the computer until the technologist specifically requests transmission by depressing a button labeled "Enter Request." In other words, the person making the entries can visually verify the entire entry and can correct an error before entering data into the computer. After visual verification, the "Enter Request" button is depressed which sends the entire request message to the computer. The request is stored in the

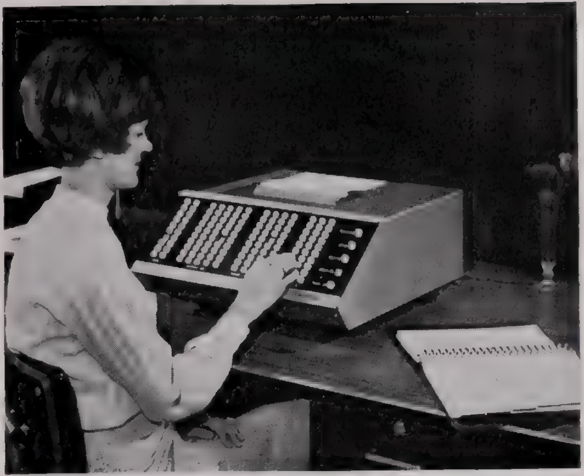


Fig. 2—This photograph illustrates how a DNA 20/20 request terminal is utilized to make rapid inquiries into the system. The operator merely enters the patient number and tests type and then depresses the "Inquire" button to obtain a seven-day historical summary report from a specific test service. This report will aid the physician in identifying abnormal trends. Similar DNA 20/20 consoles are utilized to input qualitative test data.

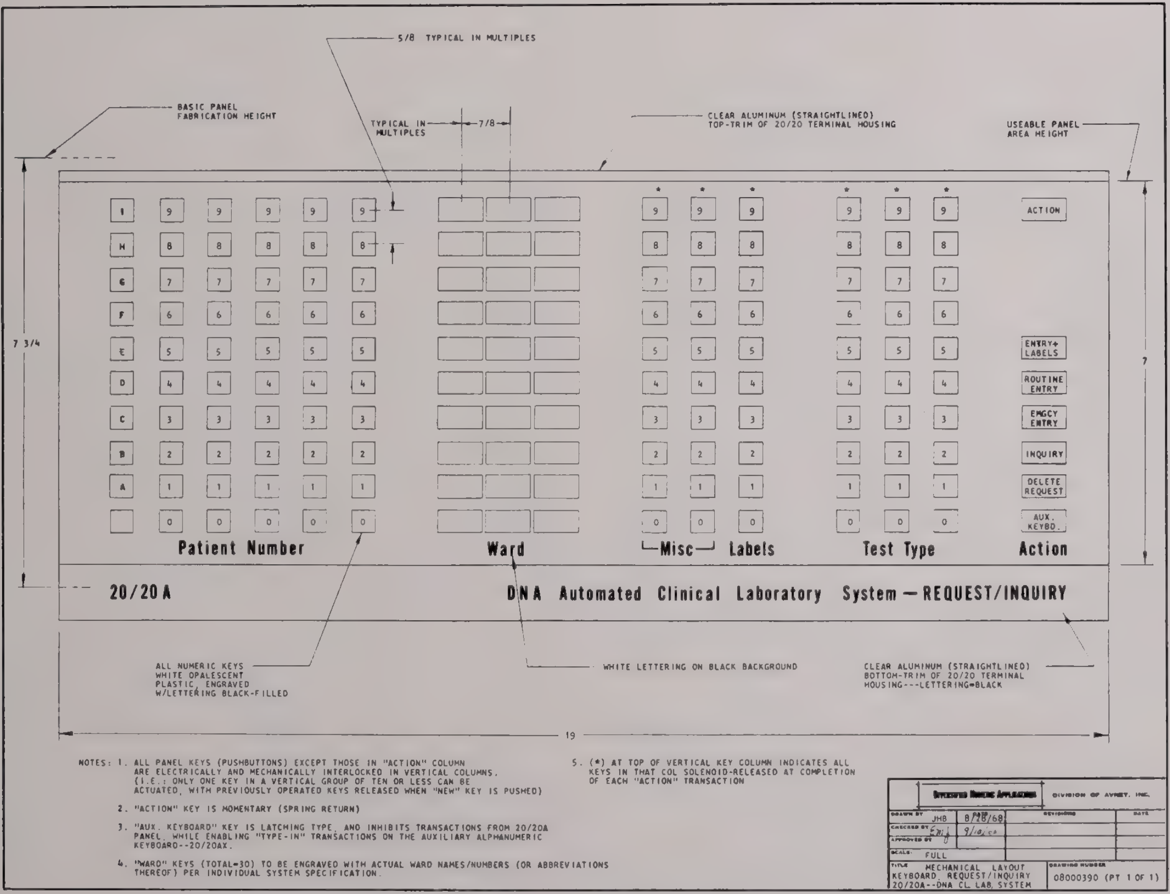

5/8 TYPICAL IN MULTIPLES
BASIC PANEL FABRICATION HEIGHT
TYPICAL IN MULTIPLES
7/8
CLEAR ALUMINUM (STRAIGHTLINED) TOP-TRIM OF 20/20 TERMINAL HOUSING
USEABLE PANEL AREA HEIGHT
7 3/4
7
I H G F E D C B A
9 8 7 6 5 4 3 2 1 0
*
ACTION
ENTRY+ LABELS
ROUTINE ENTRY
EMGCY ENTRY
INQUIRY
DELETE REQUEST
AUX. KEYBD.
Patient Number
Ward
—Misc— Labels
Test Type
Action
20/20A
DNA Automated Clinical Laboratory System — REQUEST/INQUIRY
ALL NUMERIC KEYS WHITE OPALESCENT PLASTIC, ENGRAVED W/LETTERING BLACK-FILLED
WHITE LETTERING ON BLACK BACKGROUND
CLEAR ALUMINUM (STRAIGHTLINED) BOTTOM-TRIM OF 20/20 TERMINAL HOUSING---LETTERING=BLACK
19
NOTES: 1. ALL PANEL KEYS (PUSHBUTTONS) EXCEPT THOSE IN "ACTION" COLUMN ARE ELECTRICALLY AND MECHANICALLY INTERLOCKED IN VERTICAL COLUMNS. (I.E.: ONLY ONE KEY IN A VERTICAL GROUP OF TEN OR LESS CAN BE ACTUATED, WITH PREVIOUSLY OPERATED KEYS RELEASED WHEN "NEW" KEY IS PUSHED)
2. "ACTION" KEY IS MOMENTARY (SPRING RETURN)
3. "AUX. KEYBOARD" KEY IS LATCHING TYPE, AND INHIBITS TRANSACTIONS FROM 20/20A PANEL, WHILE ENABLING "TYPE-IN" TRANSACTIONS ON THE AUXILIARY ALPHANUMERIC KEYBOARD--20/20AX.
4. "WARD" KEYS (TOTAL=30) TO BE ENGRAVED WITH ACTUAL WARD NAMES/NUMBERS (OR ABBREVIATIONS THEREOF) PER INDIVIDUAL SYSTEM SPECIFICATION.
5. (*) AT TOP OF VERTICAL KEY COLUMN INDICATES ALL KEYS IN THAT COL SOLENOID-RELEASED AT COMPLETION OF EACH "ACTION" TRANSACTION
DIVISION OF AVNET, INC.
DRAWN BY JHB 8/28/68
CHECKED BY 9/10/68
APPROVED BY
REVISIONS
DATE
SCALE: FULL
TITLE MECHANICAL LAYOUT KEYBOARD, REQUEST/INQUIRY 20/20A--DNA CL. LAB. SYSTEM
DRAWING NUMBER 08000390 (PT 1 OF 1)

Fig. 3. Request Keyboard Layout.

computer, and the terminal immediately prints a reply (Figure 4).

```
                    Request Printout

9:15  123455 Doe, John B. 4W Dr. Bland
      121 Creatinine
      123 Calcium
      128 SGOT
      131 Serum Iron
      135 Sodium
      144 Potassium
      176 CO2 Content
      177 Chloride
      178 Magnesium
9:15  987651 Jones, John J. 6C Dr. Casey
      124 Uric Acid
9:16  771502 Patient Name Not In File
9:16  771502 Borden, J. P. File Entry
9:17  771502 Borden, J. P.
      135 Sodium
      177 Chloride
          Test 188 not in file
      178 Magnesium
```

Fig. 4—Request Printout

Retrieval of Fixed Information

Notice that the first entry for a patient initiates a printout of the complete heading for that patient, including the patient's name, number, doctor, room number and other pertinent fixed information. An important feature of the system is that fixed patient data is not entered with each patient request. The computer retrieves from a file of all inpatient information stored in its auxiliary memory and updates it as patients are admitted to and discharged from the hospital. After the clerk enters the first test for a given patient she can request each additional test with a code number. The computer instantaneously replies to the entry by printing out a description of the requested tests. With this procedure, the computer can prepare an individual request summary for each patient. This can then be compared with the original request slips to assure validity.

The entry procedure can vary. For example, rather than entering all the requests centrally in the laboratory, request terminals can be located remotely at nursing stations to speed communications and minimize clerical work for laboratory personnel. Another variation would be the entry of test requests on punched cards or some other form of machine readable input.

Organization of Laboratory Activities

The next phase of the system's operation is organizing activities for the laboratory personnel. This is done by the computer. It analyzes test requests and prepares printed documents based upon this analysis. At his discretion, the laboratory director uses the master console to initiate preparation of the basic organizational reports, including the blood drawing lists, test worksheets, and specimen labels.

The Master Console

Before describing these reports let's consider the master console more carefully. The master console allows the laboratory director to completely control the operation of the computer system without performing any actions directly on the basic computer. This is an important point because the computer itself has a complex control panel designed to be used by experienced programmers. The master console, however, is a simple device; it provides the laboratory director control through a group of individually labeled function buttons. If the laboratory director wishes to prepare blood drawing lists and worksheets, he presses the buttons labeled, "Blood Drawing" and "Worksheet". The computer then proceeds to printout these reports on the high speed printer.

Blood Drawing Lists

The blood drawing list (Figure 5) contains patient name, number, room number or ward, and specimen number. The computer assigns specimen numbers and maintains an index correlating these numbers with patient numbers. In addition to blood drawing lists, the system simultaneously prepares specimen labels for each individual patient.

Blood Drawing List

Floor 4W 03/19/68

Pat. No.	Name	Specimen No.
172594	Johnson, William U.	C0505
284879	McIntosh, Barglot	C0657
869678	Bren, Maurice F.	C0137
110487	Doubler, Marlene	C0194
588827	Stromberg, James	C0977
565010	Nyberg, Oscar V.	C0747
046033	Skillings, Clyde	C0935

Fig. 5—Blood Drawing List

Specimen Labels

The labels identify the specimen by patient number, name, date, specimen number and ward location or room number and also indicate the type of container to be used for each specimen. With computer-prepared blood drawing lists and specimen labels, blood drawing becomes a thoroughly organized and controlled activity. The computer also prints worksheets for each test to be performed.

Laboratory Worksheets

The worksheet (Figure 6) includes the test name and number, specimen number, patient name and number. Room is provided for writing in results where data is not transmitted directly from an instrument to the computer. Worksheets can be generated throughout the day—with each new sheet including only those tests requested since the printout of the last worksheet.

Entry of Test Results

All of these procedures precede the actual entry and storage of test results in the computer. The next phase of system operation concerns the gathering of test results by the computer for storage and processing.

Chemistry Worksheet
Sodium Test 125

Spec. No.	Na	Name	03/19/68 Patient No.
C0137	....	Bren, Maurice F.	869678
C0194	....	Doubler, Marlene	110487
C0431	....	Hildreth. Ida T.	387301
C0505	....	Johnson, William J.	172594
C0657	....	McIntosh, Barglot	284879
C0747	....	Nyberg, Oscar V.	565010
C0935	....	Skillings, Clyde	046033
C0977	....	Stromberg, James	588827

Fig. 6—Work Sheet

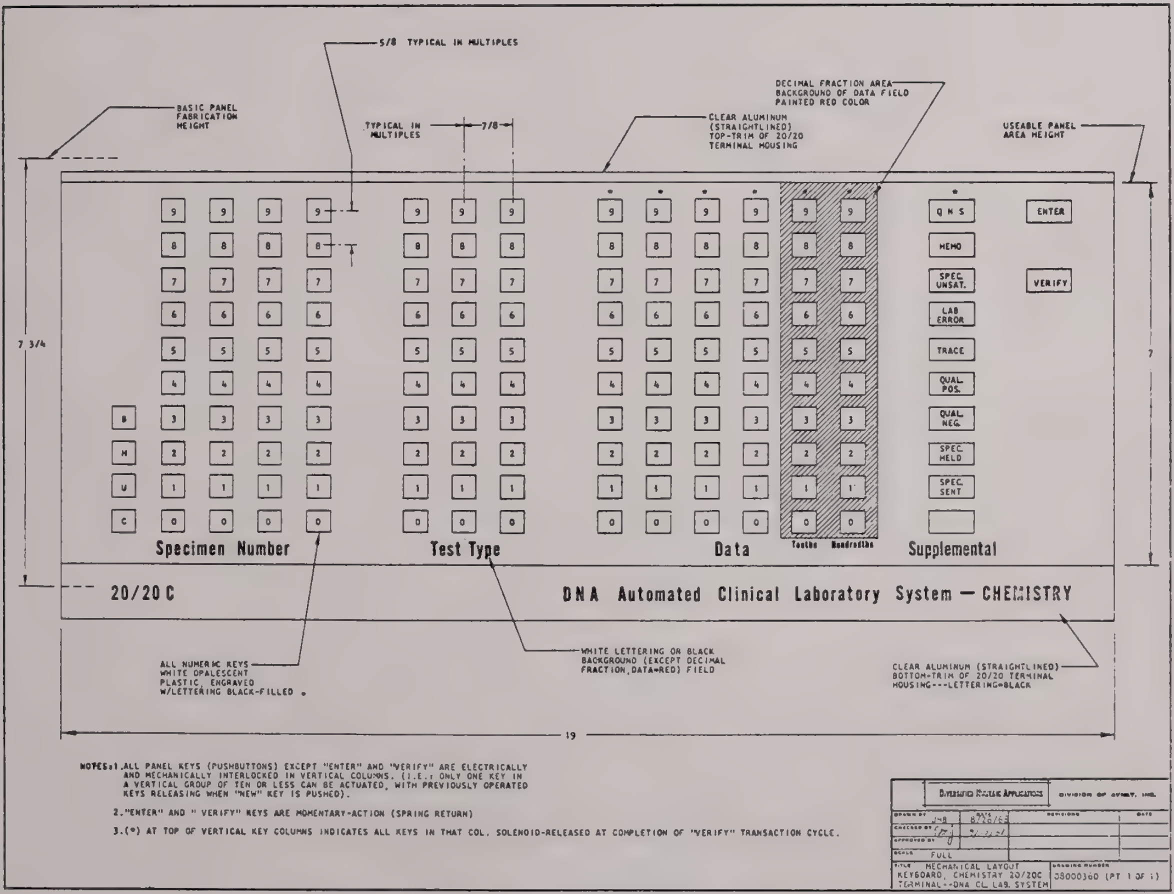

5/8 TYPICAL IN MULTIPLES
BASIC PANEL FABRICATION HEIGHT
TYPICAL IN MULTIPLES
7/8
CLEAR ALUMINUM (STRAIGHTLINED) TOP-TRIM OF 20/20 TERMINAL HOUSING
DECIMAL FRACTION AREA BACKGROUND OF DATA FIELD PAINTED RED COLOR
USEABLE PANEL AREA HEIGHT
7 3/4
7
9 8 7 6 5 4 3 2 1 0
B
M
U
C
Q N S
MEMO
SPEC. UNSAT.
LAB ERROR
TRACE
QUAL. POS.
QUAL. NEG.
SPEC. HELD
SPEC. SENT
ENTER
VERIFY
Specimen Number
Test Type
Data
Tenths
Hundredths
Supplemental
20/20 C
DNA Automated Clinical Laboratory System — CHEMISTRY
ALL NUMERIC KEYS WHITE OPALESCENT PLASTIC, ENGRAVED W/LETTERING BLACK-FILLED.
WHITE LETTERING OR BLACK BACKGROUND (EXCEPT DECIMAL FRACTION, DATA=RED) FIELD
CLEAR ALUMINUM (STRAIGHTLINED) BOTTOM-TRIM OF 20/20 TERMINAL HOUSING---LETTERING=BLACK
19
NOTES: 1. ALL PANEL KEYS (PUSHBUTTONS) EXCEPT "ENTER" AND "VERIFY" ARE ELECTRICALLY AND MECHANICALLY INTERLOCKED IN VERTICAL COLUMNS. (I.E.: ONLY ONE KEY IN A VERTICAL GROUP OF TEN OR LESS CAN BE ACTUATED, WITH PREVIOUSLY OPERATED KEYS RELEASING WHEN "NEW" KEY IS PUSHED).
2. "ENTER" AND " VERIFY" KEYS ARE MOMENTARY-ACTION (SPRING RETURN)
3. (•) AT TOP OF VERTICAL KEY COLUMNS INDICATES ALL KEYS IN THAT COL. SOLENOID-RELEASED AT COMPLETION OF "VERIFY" TRANSACTION CYCLE.
DIVERSIFIED NUMERIC APPLICATIONS
DIVISION OF AVNET, INC.
DRAWN BY JHB
DATE 8/26/68
CHECKED BY
APPROVED BY
REVISIONS
DATE
SCALE FULL
TITLE MECHANICAL LAYOUT KEYBOARD, CHEMISTRY 20/20C TERMINAL--DNA CL. LAB. SYSTEM
DRAWING NUMBER 38000360 (PT 1 OF 1)

Fig. 7—Test Result Keyboard Layout

*On-Line Auto-Analyzer®**

Test data is entered into the computer in two ways. First, certain instruments are connected directly to the computer. With digital output instruments data can be taken directly from the instrument. The technologist pushes a button which transmits the data to the computer where it is stored. With analog output instrument, the data first goes through an analog to digital converter and is then stored in the computer. With completely automatic instruments such as the auto-analyzer,® the technologist does not need to intervene once the instrument is loaded makes calculations, prints out results for inspec- with samples. The computer stores test data, tion. Finally results are ready for the completed patient report.

The Manual Test Result Console

In situations where it is either not possible or not desirable to interface an instrument directly to the computer, data is entered through the test result console, which is specially designed to provide a simple and reliable method for accurately entering test data into the system. The design of the console is similar to the request console (Figure 2), but the input keyboard layout is tailored to data entry (Figure 7).

Typically the technologist would enter a series of results for a given test, taken from the worksheet for that test. The keyboard of the terminal is designed to correspond to one line of the worksheet—which includes test number, specimen number and result. No data is transmitted to the computer until the technologist visually verifies that the right keys have been pressed and then pushes the button labeled "Enter & Reply." The entire message is then transmitted to the computer where several things occur practically instantaneously.

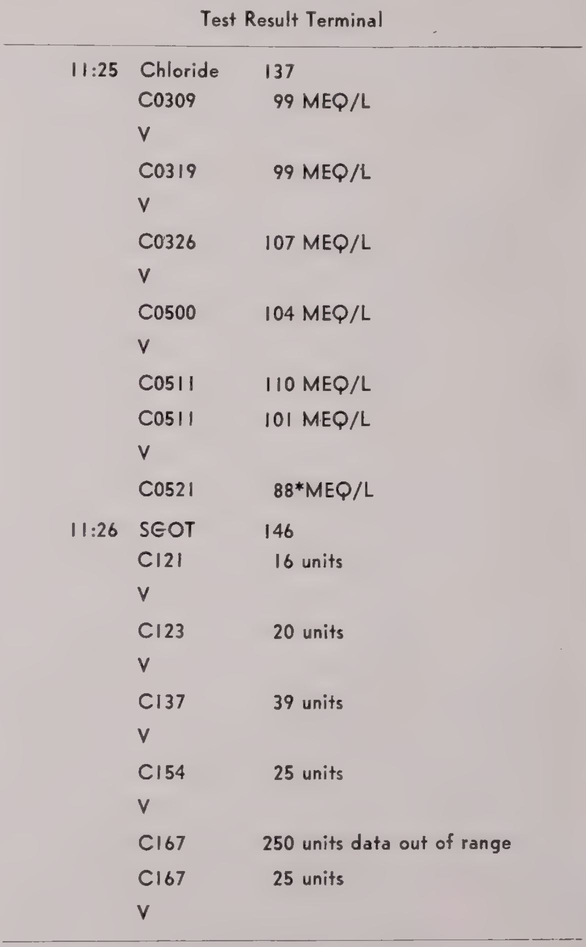
Verification of Results

First the data is checked against statistical limits to detect abnormal entries which might indicate either an operator error or a legitimate abnormal value. The computer also looks up the test name corresponding to the test number. A reply is instantaneously generated by the printer which is built into the result terminal (Figure 8).

The reply consists of the test number, the test name, specimen number, and the result. This print-out allows the technologist to verify the entry and to correct it if an error has been made. It also serves as a record for audit and control purposes. If a result exceeds certain preset limits, established for each type of test, the terminal prints a message to alarm the technologist of this fact.

Inquiry Potential

Throughout the day results are stored in the computer until all tests for a given patient are completed. However, at any time, inquiries can be made into the system, using the request console in order to obtain partial results for a given patient. Inquiries can be made either by patient's name or number. It is also possible to make inquiries directly from remote locations



```
                Test Result Terminal
11:25  Chloride    137
       C0309        99 MEQ/L
       V
       C0319        99 MEQ/L
       V
       C0326       107 MEQ/L
       V
       C0500       104 MEQ/L
       V
       C0511       110 MEQ/L
       C0511       101 MEQ/L
       V
       C0521        88*MEQ/L
11:26  SGOT        146
       C121         16 units
       V
       C123         20 units
       V
       C137         39 units
       V
       C154         25 units
       V
       C167        250 units data out of range
       C167         25 units
       V
```

Fig. 8. Result Entry Printback

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*Trademark of Technicon Instruments Corporation.

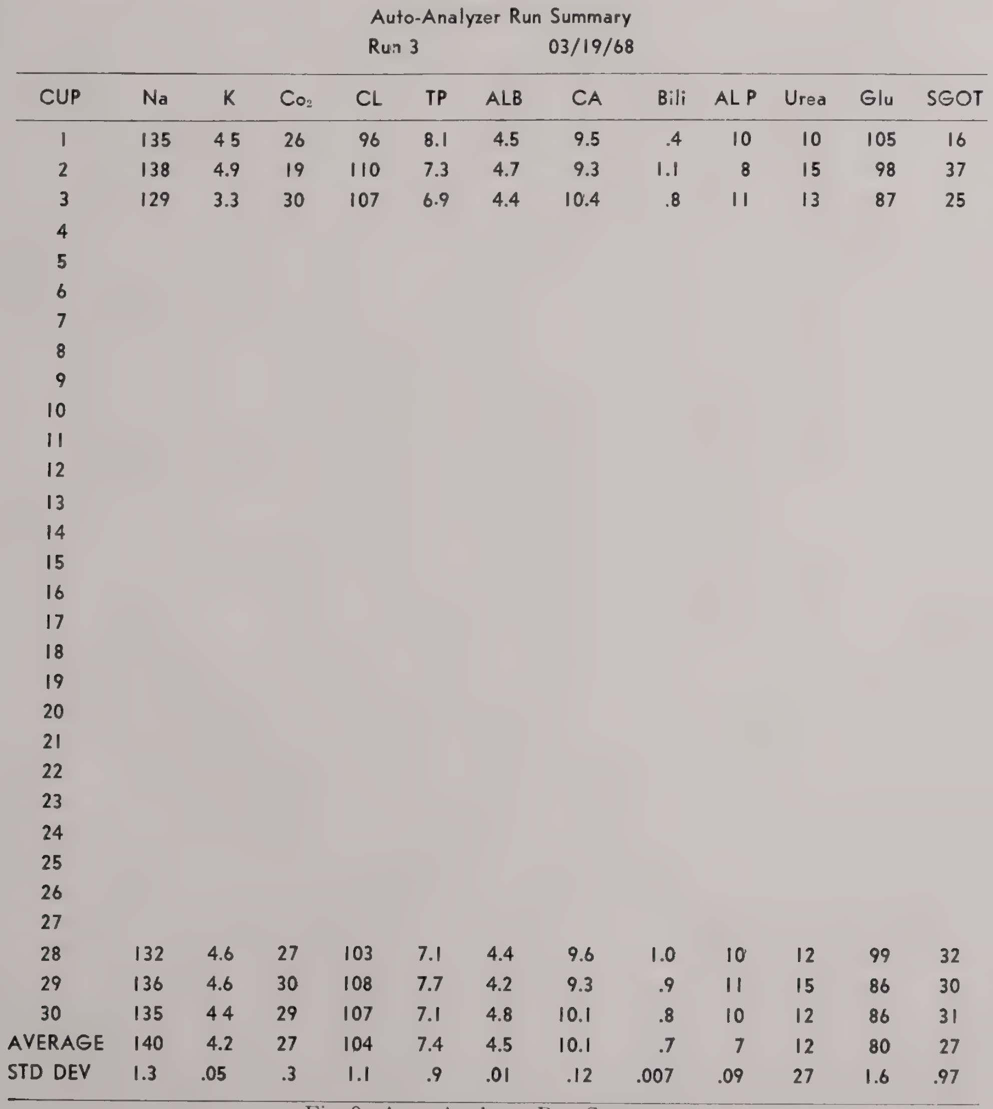
by using request consoles located at nursing stations and other central points within the hospital.

Additional Reports from the Master Console

The laboratory director can request a variety of reports by using the master console. These reports include the worksheets and blood drawing lists already described. Other reports which can be requested include:

1. Auto-Analyzer Summary (Figure 9): a printout of all completed auto-analyzer results for verification purposes.
2. Unfinished request report: a report of all tests requested but not yet completed.
3. Floor Report (Figure 10): a list of test results by patient for all patients in a given ward or other physical area.
4. Statistical Reports (Figure 11): a summary of the total number of tests performed broken down by service.
5. Chart Report (Figure 12): a report of the current day's test results for a given patient.
6. Cumulative Chart Report: the results of all previous tests for the entire week, summarized on a daily basis.

The cumulative chart report is a major benefit of the system since an entire week's results are summarized on one sheet of paper and placed in the patient chart. This speeds up the interpretation of data by the physician and minimizes the possibility of losing individual results. Should a report be lost, an entire



```
                            Auto-Analyzer Run Summary
                            Run 3               03/19/68

CUP       Na     K     Co2    CL    TP    ALB    CA     Bili   AL P   Urea   Glu   SGOT

1         135    4 5   26     96    8.1   4.5    9.5    .4     10     10     105   16
2         138    4.9   19     110   7.3   4.7    9.3    1.1    8      15     98    37
3         129    3.3   30     107   6.9   4.4    10.4   .8     11     13     87    25
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28        132    4.6   27     103   7.1   4.4    9.6    1.0    10     12     99    32
29        136    4.6   30     108   7.7   4.2    9.3    .9     11     15     86    30
30        135    4 4   29     107   7.1   4.8    10.1   .8     10     12     86    31
AVERAGE   140    4.2   27     104   7.4   4.5    10.1   .7     7      12     80    27
STD DEV   1.3    .05   .3     1.1   .9    .01    .12    .007   .09    27     1.6   .97
```

Fig. 9. Auto-Analyzer Run Summary

week's report can be duplicated by the computer in seconds.

Growth Potential of the System

Although the system described is a stand-alone system operating entirely within the confines of the laboratory, it has been designed to facilitate two avenues of projected growth. First, the requirements of the laboratory are sure to change, and the modular design of the computer system accommodates these changes by allowing the simple addition of new instruments and new programs. Second, the system anticipates the growing importance of communications within the hospital and has adequate provision for handling a large number of communication terminals located outside of the laboratory for direct input of test requests and local printout of patient reports.

The Total Hospital Information System

Even more important, however, the system anticipates that other small computer systems will be installed in different areas of the hospital. These systems, like the laboratory system, will at first be independent. But at some future time, as more is learned about the information flows among the various hospital departments, these independent systems will be interconnected to form a total hospital information and communications network. This concept of a number of small computers interconnected to form a network is a new one, but a concept rapidly gaining acceptance as the most practical method by which small and medium-sized hospitals can commence upon a program of clinical and administrative automation on a realistic evolutionary basis.

```
                         Floor Report
         Floor 4W                                   03/19/68
-------------------------------------------------------------
Pat. No.                  Name                     Spec. No.
-------------------------------------------------------------
172594                    Johnson, William U.         505
  Sodium                    135 MEQ/L
  Potassium                 4.5 MEQ/L
  CO2 Content                26 MEQ/L
  Chloride                   97*MEQ/L
  Total Protein             8.1 GM/100 ML

284879                    McIntosh, Barglot           657
  T.I.B.C.                  275 MCG/100ML
  Calcium                   9.5 MG/100ML
  Bilirubin                  .4 MG/100ML

869678                    Bren, Maurice F.            137
  Alk Ptase                  16*K-A Units
  Urea Nitrogen              10 MG/100 ML
  Glucose (Fasting)         101 MG/100 ML
  SGOT                       16 Units
  Sodium                    141 MEQ/L
  Potassium                 4.8 MEQ/L
  CO2 Content                31*MEQ/L

110487                    Doubler, Marlene            253
  Chloride                  100 MEQ/L
  Total Protein             7.6 GM/100ML
  Magnesium                 2.0 MG/100ML

588827                    Stromberg, James            977
  Calcium                  11.5*MG/100ML
  Bilirubin                  .7 MG/100ML

565010                    Nyberg, Oscar V.            747
PL. Cortisol                 20 MCG/100ML
-------------------------------------------------------------
  *Out of normal range
```

Fig. 10. Floor Report

```
                     Clinical Laboratories
                        Monthly Report
-------------------------------------------------------------------
Month: March, 1968                          Date: April 5, 1968
Section: Bio-chemistry                      Submitted by:

Type          In      Out                                Total for
of Test     Patient Patient Emp E.R. OB NSY Peds  this month
-------------------------------------------------------------------
Glucose
Urea Nitrogen
Creatinine
Total Protein
A/G Ratio
Uric Acid
Bilirubin
Thymol Turbidity
Acid Phosphatase
Cholesterol
Bromulphalein
Transaminase SGOT
Transaminase SGOT
Phosphorus
Calcium
Carbon Dioxide
pH
Sodium
Potassium
Chloride
Lipase
Amylase
Fibrinogen
Serum Iron
Total Lipids
-------------------------------------------------------------------
```

Fig. 11. Statistical Report

Summary

The Diversified Numeric Applications Clinical Laboratory System is a low cost, 100% on-line, random access data processing system designed specifically for the clinical laboratory. DNA's exclusive functionally designed clinical laboratory data terminal permits complete operation of the system by existing laboratory personnel. Laboratory personnel interact with the system entirely through foolproof terminals and are never required to change tapes or perform any operation directly on the basic computer.

The Diversified Numeric Applications laboratory system is provided as a complete package that is customized to meet the needs of the particular laboratory. The DNA system package includes hardware, all laboratory application programs, documentation, training, systems installation and maintenance.

Neil I. Fishman*
Robert L. Strom, M.D.†
Minneapolis, Minnesota

Chart Report

Bren, Maurice F. — Date 03/19/68
869678 4W

Test	03/16/68	03/17/68	03/19/68
CO_2 Content	26	25	98
Chloride	97	96	98
Sodium	135	136	140
Potassium	4.5	4.8	4.1
Calcium			
Magnesium			
In. Phosphate			
Alk Ptase	16		15
L D.H.	138		145
S.G.O.T.	16		20
Bilirubin Tot	0.4		0 5
Bilirubin Dir			
B.S.P.			
Total Protein			
Prot. Electro			
Total Lipids			
Cholesterol			
Creatinine	0.6		0.6
Urea Nitrogen	7		10
Uric Acid		4.3	
Glucose Tol.			
Serum Iron			

Fig. 12. Chart Report

---

*President, Diversified Numeric Applications, Minneapolis, Minnesota.

†Associate Pathologist, Hennepin County General Hospital.

Social State Medicine

In the area of nutrition and health it would be relatively easy to produce economically in factories a "man chow" which would supposedly be the perfect food for the average man. This "man chow" idea is completely unrealistic. It will not work, because of the biochemical individuality of man.

The Food and Drug Administration, at least until very recently, has done some of its planning on the basis of the hypothetical average man and has sought to regulate the marketing of medicinal substances on this basis. This cannot work because of the hard facts of biochemical individuality. People do not react in a uniform manner, either to drugs or to nutritional factors.

Roger J. Williams, The Freeman, January 1969.

Two things we ought to learn from history: one, that we are not in ourselves superior to our fathers; another, that we are shamefully and monstrously inferior to them, if we do not advance beyond them.—T. Arnold

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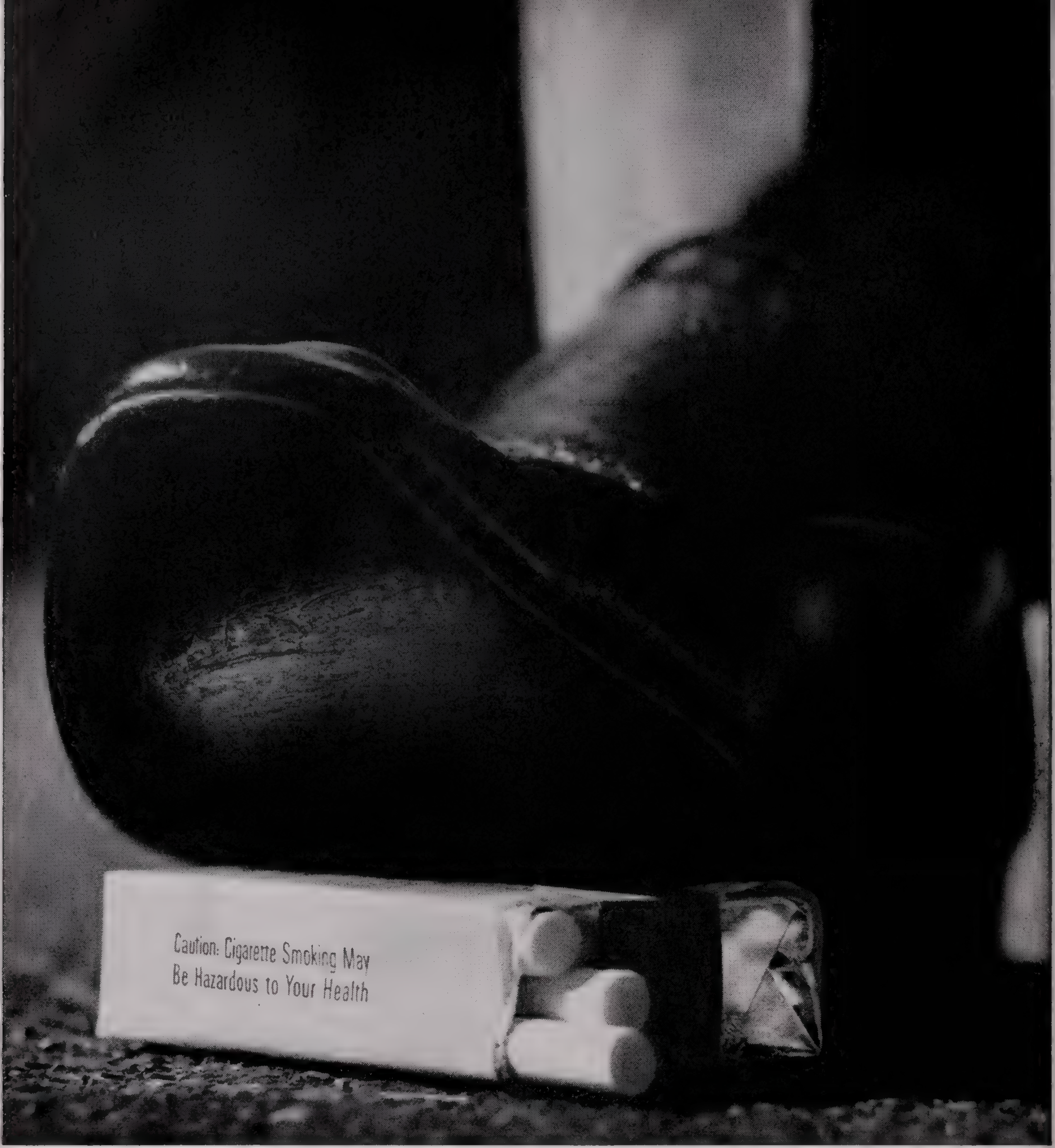
It is easier to make certain things legal than to make them legitimate.—Chamfort


Caution: Cigarette Smoking May
Be Hazardous to Your Health

If you give up cigarettes, you might gain a few pounds.

(And also a few years.)

The plain, unfiltered fact is that people who smoke cigarettes get lung cancer a lot more frequently than nonsmokers.

And lung cancer can finish you.

Before your time.

We'd rather have you stay alive and in good health.

Because even if you do gain a few pounds, you'll have the time to take them off.

american cancer society

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Abstracts, Briefs and Commentaries

GASTROENTEROLOGIC COMPLICATIONS OF ANTICOAGULANT THERAPY

Concomitant with the therapeutic use of anticoagulants "new diseases of medical progress" have developed, related to the physiologic and pathologic variability in humans. The major and most feared side effect has been hemorrhage.

"Manifestations of bleeding such as melena, hematemesis, and hematochezia may be harbingers of serious underlying disease." These complications may be sudden and demand immediate and appropriate therapy. To persist in anticoagulant therapy when a patient is bleeding into the intestinal lumen, intra-abdominal viscera, or rectus muscle may be disastrous; to discontinue anticoagulant therapy may invite new thromboembolic episodes. A list of complications associated with anticoagulant therapy is revealing.

The incidence of hemorrhage is reviewed in nine reported series. In non-hospitalized patients on anticoagulant therapy the incidence of hemorrhage is from 5 to 48%. Other reports vary from 2 to 10%. The incidence of major hemorrhage varies from 0.8 to 12%. Russek and Zohman stated that about 50% of 228 medical specialists observed serious hemorrhage following anticoagulant therapy for acute myocardial infarction.

Approximately 3 to 4% of patients on anticoagulant therapy have gastrointestinal bleeding. A questionnaire by Russek and Zohman revealed 30 reports of death due to exsanguination after gastrointestinal bleeding. Two of four patients with inoperable cancer of the stomach had hematemesis when taking anticoagulants. One woman is reported to have bled from peptic ulcer after taking dicumarol for thrombophlebitis. One should suspect malignancy in cases having gastrointestinal bleeding if the prothrombin time is in the therapeutic range.

Several authors reported lesions in the gastrointestinal tract that bled in patients who were on anticoagulants. The most common lesions that bled were peptic ulcer, hemorrhoids, cancer, diaphragmatic hernia, and diverticula. Lesions found included peptic ulcer and carcinoma of the colon. Nathan and Kimball received 1,867 replies to a questionnaire; 128 reported unsuspected tumor in patients who bled while on anticoagulants. Zweifler's series reported that seven of 12, who bled when the prothrombin activity was greater than

15%, had organic lesions; in the 12 with a prothrombin less than 15% no occult lesion was found.

Patients with T-tube drainage of the common duct are sensitive to oral anticoagulants and more apt to hemorrhage if pancreatic disease is present.

Bleeding into the bowel wall occurred in 63 cases; in the small bowel in 54 cases; in both the small and the large bowel, in five cases; and in the large bowel only, in three cases.

Most authors have stated that bleeding starts in the submucosal layer. Extension to the mucosa causes varying degrees of obstruction and blood in the lumen. Dissection toward the serosa results in decreased peristalsis and possible bleeding into the mesentery and peritoneal cavity, causing volvulus and obstruction. Onset may be gradual, accompanied by cramping pain, distention and vomiting. Bleeding may be also present in the skin, gums, urine and feces.

X-ray examination may reveal intra-intestinal and intramural hemorrhage, characteristic fluid level and obstruction. Blood may migrate to the flanks by following fascial planes.

Nonoperative medical regimens consist of I.V. fluids with small doses of vitamin K. These patients are often elderly and are a poor surgical risk because of arteriosclerotic disease. Thirty of 63 patients were managed successfully without surgery. Seven of 33 patients were explored for possible bowel viability; 33 had abdominal operations; 24 had resections, and two had bypass procedures. There were five postoperative deaths, three secondary to myocardial infarction. A fourth patient died eight days postoperatively from gangrene of the bowel at the site of the previous resection. The fifth patient, a 75-year-old male with three previous myocardial infarctions, died five days postoperatively. Autopsy revealed intramural hemorrhage extending from the small bowel to the sigmoid colon.

Each patient must be watched for continuing hemorrhage, unresolved obstruction, bowel perforation, or persistent symptoms which demand laparotomy.

Hemorrhage may be retroperitoneal, 12 cases being reported from the University of Pennsylvania, or intra-abdominal, involving the pancreas, ovarian cysts or adnexia, with massive accumulation of blood in the peritoneal cavity. Jaundice due to liver injury has been reported as the direct effect of anticoagulant drugs.

Complications resulting from anticoagulant therapy must be anticipated. The effects may be minor or major. Medical management may be adequate; but surgery may be imperative if intra-abdominal hemorrhage is not controlled. Gangrenous organs or bowel demand surgery which carries with it a high risk. Reports all seem to favor medical treatment when possible. This publication in the Mayo Clinic Procedures is most valuable to both internist and surgeon. The authors should be complimented on its presentation.

Stanley R. Maxeiner, Sr., M.D.
Minneapolis, Minnesota

Babb, Richard R.; Spitell, John A., Jr. and Bartholomew, Lloyd G.: Gastroenterologic Complications of Anticoagulant Therapy. Mayo Clin Proc October, 1968.

CONGENITAL HEART DISEASE—SURGICAL RESULTS

Surgical correction of many congenital heart defects can be carried out with a high degree of safety. Techniques of extracorporeal circulation, even for quite small children, are well standardized and accompanied by low risk. The pathologic anatomy of most congenital cardiac anomalies has been well described, and techniques for correction of the more common varieties can be expected to produce excellent results.

We have operated upon twenty-six patients for correction of various congenital cardiac anomalies. The pathology encountered is indicated in Table 1. Atrial septal defect, with or without partial anomalous venous return, was the most common lesion. Two highly unusual anomalies are also included in this group, namely "parachute mitral valve" and congenital diverticulum of the left ventricle. All of these patients were operated upon by open intracardiac techniques. Although one was quite elderly (i.e., atrial septal defect—age 76), most were children or young adults. Their ages ranged from 1½ years to 76 years; three were two years of age or younger at the time of surgery. There were no operative deaths and all twenty-six patients are currently alive and well.

Since the first ventricular septal defect was repaired in 1954 by cross circulation, great strides have been made in the safety with which open heart surgery can be accomplished. The techniques of extracorporeal circulation have undergone refinement to the extent that careful, deliberate repair is attended with low risk even in the very young patient. Heart block, air embolus, residual shunt and uncontrollable bleeding, which plagued the cardiac surgeon of a decade ago, are problems that can now largely be avoided. The more common congenital cardiac anomalies such as atrial septal defect, with or without partial anomalous venous returns, partial A-V canal, pulmonary stenosis, ventricular septal defect and tetralogy of Fallot can all be treated by safe, well standardized techniques with excellent results.

Joseph C. Kiser, M.D.
Theodore A. Peterson, M.D.
Frank E. Johnson, M.D.
Minneapolis, Minnesota

TABLE
Summary of Congenital Cardiac Anomalies Operated Upon

ASD (secundum type)	13
(with PAVR*)	3
Partial A-V Canal	2
VSD	2
Tetralogy of Fallot	2
Pulmonary Stenosis	1
Diverticulum of Left Ventricle	1
Subaortic Stenosis (Localized)	1
Congenital Mitral Stenosis	1
	26

*PAVR—partial anomalous venous return

CAN BREAST CARCINOMA BE ANTICIPATED?

Potter et al. have analyzed a series of 110 cases upon whom biopsies had been done for benign lesions 16 to 20 years prior to the period of study. In this study they found that five times as many patients who had been biopsied for benign lesions developed carcinoma of the breast but that this had no relationship to the specific pathologic process in the benign biopsy. It did have, however, a relationship to the years at risk.

These findings support a recommendation that all women who have biopsies for a benign lesion of the breast should have periodic checkups since carcinoma develops with much higher frequency in these women.

Editor's Note: Perhaps it also suggests that adenomammectomy would be a desirable procedure for all biopsies.*

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*See Minnesota Med 51:1325, 1968.

SONS OF ALCOHOLICS

To obtain indirect evidence regarding the personality of potential alcoholics, sons of alcoholic men were studied by a 36-item behavioral questionnaire constructed to measure personality traits common in alcoholics. Forty-one sons of alcoholics were compared with 123 matched controls by classroom teachers. Contrary to the hypothesis tested, sons of alcoholics were rated less personable and more overtly aggressive than the controls. The results were interpreted as showing a passive-aggressive personality preceding and possibly leading to alcoholism.

Courtesy of References and Reviews
Journal of the American Medical Association

Aronson, H., and Gilbert, A.: Arch Gen Psychiat 8:235, 1963.

Blains

Exodus IX 8-11: And the Lord said unto Moses and unto Aaron, Take to you handfuls of ashes of the furnace, and let Moses sprinkle it toward heaven in the sight of the Pharaoh.

And it shall become small dust in all the land of Egypt, and shall be a boil breaking forth with blains upon man and upon beast, throughout all the land of Egypt.

And they took ashes of the furnace and stood before Pharaoh and Moses sprinkled it upward towards heaven; and it became a boil breaking forth with blains upon man and upon beast.

And the magicians could not stand before Moses because of the boils; for the boil was upon the magicians and upon all the Egyptians.

Derivatively Speaking

Measles—from Middle English *maseles* (little spots)

Special Article

The Relationship of Neonatal Nutrition to Brain Growth*

HAROLD W. HERMANN, M.D.†
Evansville, Indiana

THIS MONOGRAPH presents in abbreviated form some recent discoveries in the relationship of neonatal nutrition to brain growth and development. Animal data will be given first, to be followed by a limited amount of information pertaining to the human.

Calculating Growth

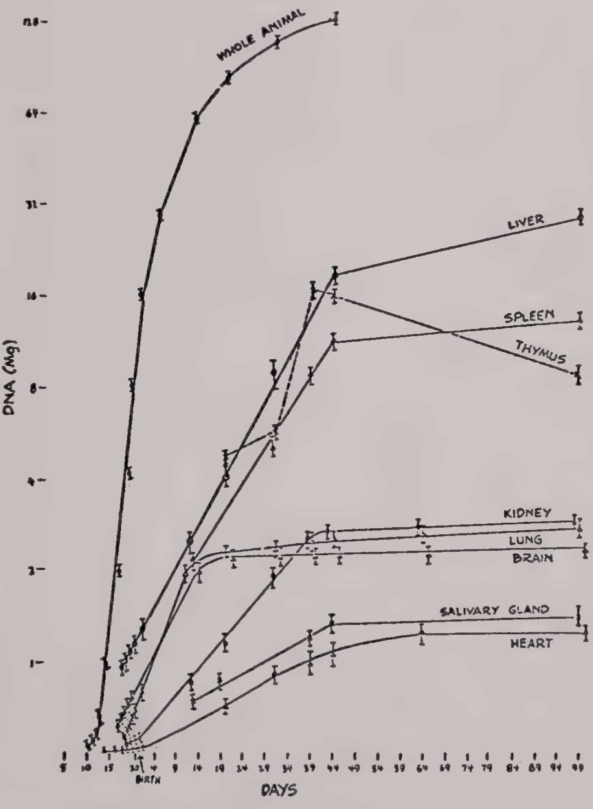
In 1962 Enesco and Leblond[1] published their findings that each diploid nucleus cell of the rat contains 6.2 micro-micrograms of deoxyribonucleic acid. It has since been determined that the amount of deoxyribonucleic acid per nucleus cell is species-constant. Therefore, the number of cells per organ for any species can be calculated at any point of growth and development upon determination of the total organdeoxyribonucleic acid.

$$\text{Cell number} = \text{number of nuclei (millions)} = \frac{\text{total organ deoxyribonucleic acid in mg.} \times 10^3}{6.2}$$

The weight per nucleus can then be determined by dividing the total organ weight by the number of nuclei.

$$\text{Cell weight estimate} = \frac{\text{total organ weight (gm.)} \times 10^3}{\text{number of nuclei } 10^6}$$

Winick and Noble[2] have shown that deoxyribonucleic acid in each body organ reaches a maximum early in development of the animal at a time characteristic for that organ and does not increase during further growth. Early prenatal growth in the rat proceeds entirely by cell division; the deoxyribonucleic acid, weight,



DNA (mg) during normal growth in the rat. Points represent mean values for at least ten animals or organs. I represents range.

Figure 1*

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*Presented at the Northwestern Pediatrics Society Annual Meeting, Hudson, Wisconsin, September 27, 1968.

†Medical Research Department, Mead Johnson Research Center.

*Quantitative Changes in Deoxyribonucleic Acid, Ribonucleic Acid, and Protein during Prenatal and Postnatal Growth in the Rat," Myron Winick and Adele Noble, Developmental Biology, Vol. 21, December, 1965.

and protein all increase proportionately with a constant cell size resulting. However, after birth, the rate of deoxyribonucleic acid synthesis (cell division) decreases at different times for various organs. Cell size increases with increased protein accumulation as the cell division rate decreases. More specifically, in the rat, growth from ten days after conception to maturity occurs in three phases: first, a rapid cell division with the cell size constant (period of deoxyribonucleic acid production only); second, an increase in cell size and cell number (period of deoxyribonucleic acid production and protein accumulation); and third, an increase in cell size only (period of protein accumulation only).

Maximum Growth

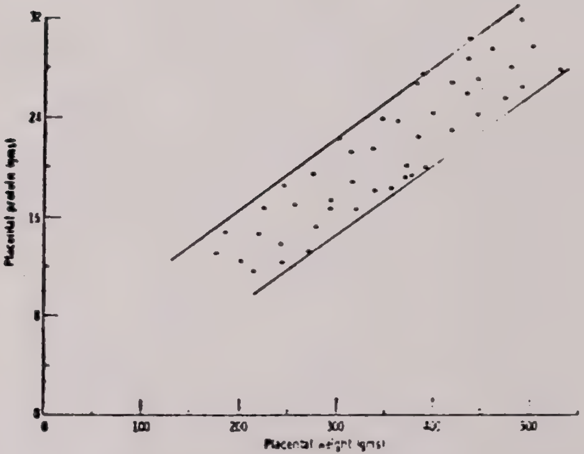
Winick and Noble have also shown that during the active period of growth in the rat deoxyribonucleic acid, ribonucleic acid, and protein increase at a specific rate for each organ for a constant period; growth stops when the total organ weight or protein reaches a constant (Figure 1). In rats the brain and lungs reach their maximum number of cells on day seventeen after birth. The other body organs continue to develop new cells until about the 42nd day of life.

Effect of Limiting Calories and Protein

It has been shown in the rat that limiting calories and protein during the first 21 days of life (period of organ development by cellular division) to about one half of normal requirements results in dwarfism with a permanent reduction of cell numbers (deoxyribonucleic acid) in all organs. Analysis of all organs shows a parallel reduction in the deoxyribonucleic acid, ribonucleic acid, and cell protein composition, and subsequent adequate nutritional feeding reveals these changes to be irreversible. A similar nutritional deprivation during only the second 21-day period of life (first three weeks postweaning) results in developmental retardation in both cell number and organ size in all organs except the brain and lungs, with a reduction in deoxyribonucleic acid, ribonucleic acid, and cell protein in these affected organs. These changes are also irreversible with subsequent full nutritional support. Finally, a 50% deprivation of calories and protein during the third 21-day period of life (after all cell division is completed) results in reduced cell size but no reduction in cell number. The cell size becomes normal with adequate subsequent nutrition.

Semistarvation During Gestation

Chow and Lee[3] have confirmed that the



Placental protein versus placental weight.

Figure 2*

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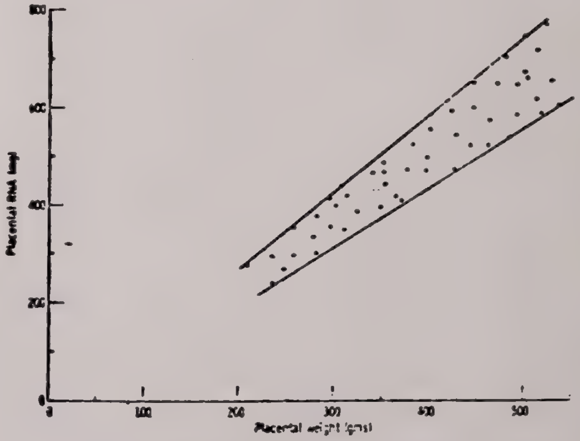
*Myron Winick, Anthony Coscia, and Adele Noble: Cellular Growth in Human Placenta. Pediatrics, Vol. 39, February 1967.



Placental RNA versus placental weight.

Figure 3*

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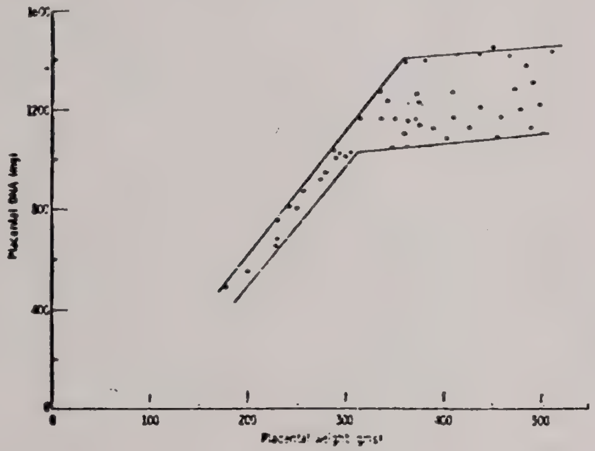
*Myron Winick, Anthony Coscia, and Adele Noble: Cellular Growth in Human Placenta. Pediatrics, Vol. 39, February 1967.

offspring of rats semi-starved during gestation and lactation by limiting the food and protein of their mother in pregnancy or by weaning large numbers of young with one mother are permanently growth-stunted and show metabolic defects. They also have a decreased efficiency for food utilization with a significant wastage of amino acids via the urinary tract.

Winick and Noble[4] have further shown that the rat's placenta growth pattern is similar to that of other organs; no further deoxyribonucleic acid is formed by the placenta after the seventeenth day of gestation. Thereafter, additional growth in size of the placenta is accompanied by increase in ribonucleic acid or of ribonucleic acid and cell protein. They[5] have also demonstrated comparable results from the analysis of fifty normal human placentae from various gestation periods. The placental weight, protein (Figure 2) and ribonucleic acid (Figure 3) continued to increase linearly until term. However, the rate of increase in placental deoxyribonucleic acid (Figure 4) rapidly declined when the placenta weighed approximately 300 gm. or the fetus 2300 gm. Thus, cell division of the human placenta stops at approximately the eighth month of gestation.

The Human Brain

In the human, deoxyribonucleic acid increases in the brain cells until approximately six



Placental DNA versus placental weight.

Figure 4*

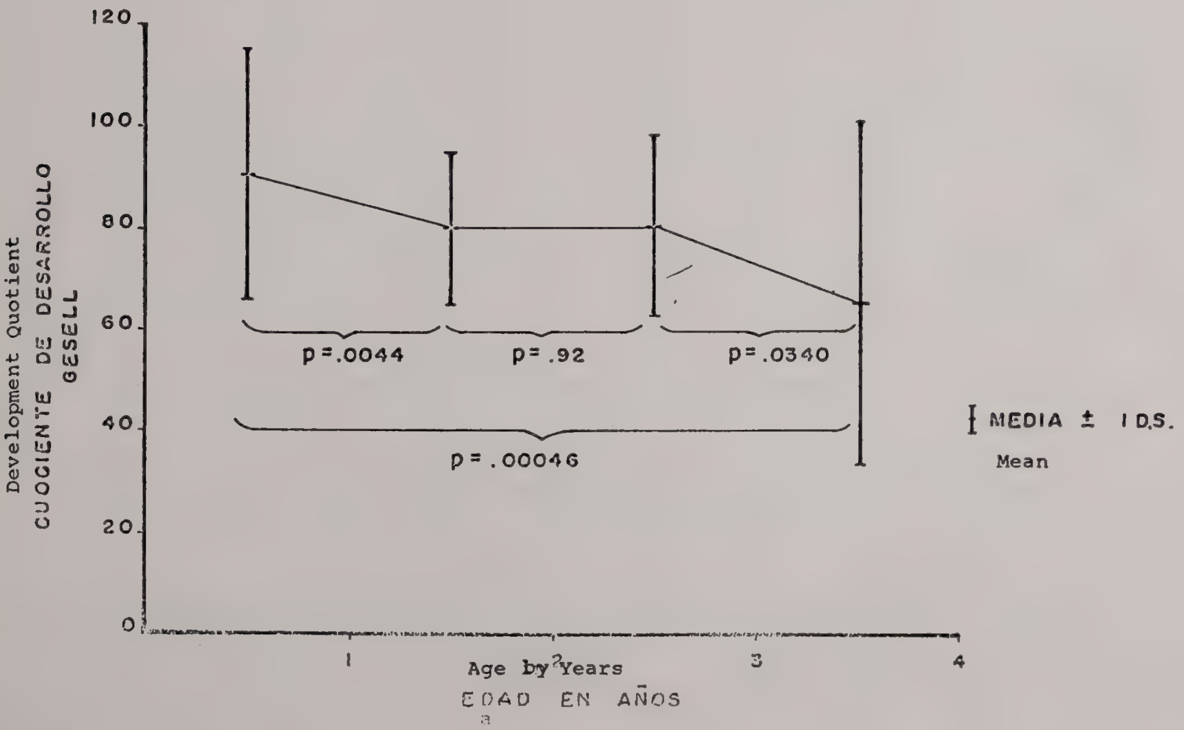


Figure 5

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*Myron Winick, Anthony Coscia, and Adele Noble: Cellular Growth in Human Placenta. Pediatrics, Vol. 39, February 1967.

months of age. Organ weight, ribonucleic acid, and cell protein continue to increase in a linear fashion for over twelve months. By analysis of a limited number of human infants' organs, Winick[6] has shown that calorie and protein malnutrition in the first three to six months of life results in a reduction of deoxyribonucleic acid. Ribonucleic acid and protein per cell were normal. The deoxyribonucleic acid reduction correlated closely with the reduction in body weight when the infant had been malnourished since birth.

Vitale's[7] studies in Colombia show a progressive decrease in intellectual ability (as measured by the Gesell method) of infants malnourished during early infancy (Figure 5).

Thus it has been shown that deoxyribonucleic acid synthesis to make all of the cells of the mature brain, whether in rats, pigs, or humans, requires a certain minimum of calorie and protein availability during pregnancy and early infancy.

Conclusions

From these preliminary data, intensive effort is required to assure an adequate supply of calories and protein for the neonate and infant. Where a country's total food resources are inadequate for the entire population, upgrading of the society demands that preferential nutritional sustenance be allocated to the infants. I am aware that concomitant re-education of the mothers may be needed to make the implementation feasible. But the rewards for an underdeveloped country's meeting this challenge would be predictably evident in *one* future generation.

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Experience is not what happens to a man. It is what a man does with what happens to him.—Aldous Huxley

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A man must (as the books on success say) give "his best;" and what a small part of a man "his best" is! His second and third best are often much better.—Chesterton

---

Man is a gregarious animal, and much more so in his mind than in his body. He may like to go alone for a walk, but he hates to stand alone in his opinions.—Santayana

History of Medicine

Development of Controlled Cardiac Pacemaking

ONE OF THE FIRST recorded cases of the use of electricity occurred in the year 15 A.D. when a freed slave of Tiberius Caesar, suffering from gout, stepped on a flat medium-sized fish, received a severe shock and, the story goes, was cured.*

Controlled electrical stimulation of the myocardium has become a reality during the last two decades, the major breakthroughs being the development of the concept of direct myocardial stimulation by an attached electrode, the transistor and solid-state electronics. Prior to this, experiments involving stimulation of the heart, nerves and muscles were carried out over a 200-year span following initial experiments by Luigi Galvani.[1]

Electrical Shock

The experimental and therapeutic use of electrical shock on living tissue was published by Giovanni (John) Aldini, the nephew of Galvani, in 1819.[2] He described his studies done on fresh cadavers and mentioned two cases contained in the register of the Royal Humane Society of Great Britain (for the years 1774 and 1787) where electrical shocks had seemingly restored life. The first of these described "a child, three years old, who fell from a one pair of stairs' window upon the pavement and was taken up without signs of life. A medical practitioner being sent for declared that nothing could be done, and that the child was irrevocably dead; but a gentleman having proposed a trial of electricity, the parents consented. At least 20 minutes elapsed before he could apply the shock, which he gave to various parts of the body without any appearance of success. On directing a few shocks to the chest, a small pulsation became perceptible, and soon after the child began to sigh and to breathe, though with great difficulty; in about 10 minutes, it vomited. A kind of stupor remained for some days; but the child was restored to perfect health and spirits in about a week."[2]

The second case involved "a lad in perfect health, who fell from a stairs' window into an area and was taken up to all appearance dead. Upon the strictest examination, no mark of violence could be discovered either upon the head or any other part. After a variety of means had been tried by a surgeon without effect, the lad was pronounced dead and sent home. A gentleman (past whose house he was carried), happening to inquire into the circumstances of the case, wished to try the effect of electricity. After four small shocks had been given, the lad showed some signs of life; and with further shocks, he gradually recovered, so that in less than two hours, he was able to walk about the house."[2]

The electrical current in Aldini's experiments was generated from a crude battery consisting of zinc plates coated with copper and placed in an acid solution. Current was then conducted through two "leads" to the subject, the areas of electrode attachment having been moistened with salt water.

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*Hammond, B. J.: A History of Electric Therapy. Part I. World Med Elect Instru 3:44, 1965.

For the next 100 years, cardiac stimulation by electrical currents was carried out via the nervous system rather than by direct myocardial excitation. In 1867 Walshe[3] stated that "Valentine, Henle, Budge and others have distinctly shown that the heart's action may be re-excited, after stoppage by galvanic stimulation of the roots of the spinal accessory nerve, of the first four cervical nerves, and of the sympathetic filaments belonging to the organ." In 1883, Professor William Erb at the University of Leipzig,[4] stimulated the vagus nerve in the neck to treat cardiac arrhythmias with "good results."

Other physicians during this period advocated electrical shock as a treatment for all human ailments. A book that effected this thinking was a "Handbook for General Practioners" written by Dr. E. H. Monell[5] (1897), which described the use of electric currents in such diverse conditions as mental derangements, leiomyomata uteri, and spinal meningitis occurring after a fall.

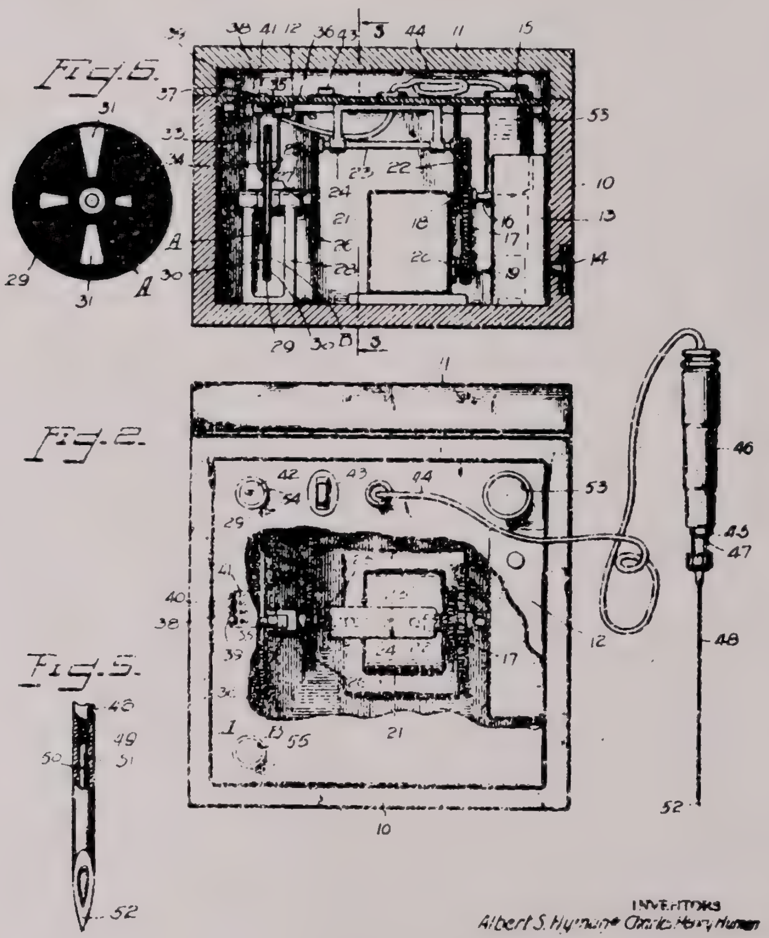
Fig. 6.
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Fig. 5.
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INVENTORS
Albert S. Hyman & Charles Henry Hyman

Figure: Photograph of a patent for an "Artificial Pace Maker for the Heart" filed by Albert and Charles Hyman* on March 12, 1930, and granted on June 13, 1933. This unit (weighing 7.2 kg.) produced cardiac contractions by sending an electrical impulse through a needle (bipolar in type) placed percutaneously into the myocardium. The thinking of these investigators (far in advance of their time) lay dormant for almost twenty years until the development of solid-state electronics made clinical use of such devices possible.[12]

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*Head, Mechanical Laboratory, Witkin Foundation.

The Needle Electrode

In 1932 Hyman,[6] while investigating the ability of a needle prick to stimulate and revive a heart in asystole, artificially produced systolic contractions by means of an electrical current flowing through a needle electrode placed percutaneously directly into the myocardium. His apparatus (weighing 7.2 kg.) consisted of a magneto generator which created the stimulating current. This could be rewound by a spring motor without affecting the output from the generator. Current then passed down the percutaneously inserted needle (bipolar in type) to the tip where it came in contact with the myocardium (Figure). He made mention of the successful resuscitation of an infant, reported by Gould at the Medical Congress in Sydney, Australia, in 1929,[6] by means of electrical stimulation of the heart through a percutaneous needle electrode and suggested the more frequent clinical use of this artificial electrical pacemaking technique.

While Marmorstein[7] first described electrical endocardial stimulation of the dog heart in 1927 by means of an intravenous electrode, this approach was not used again until 1951 when Callaghan and Bigelow[8] experimented successfully with direct external and intravenous endocardial stimulation of the sino-atrial node and right atrium by means of unipolar and bipolar electrodes in hypothermic and normothermic dogs. Finally, Furman[9] in 1959 made clinical use of this technique, describing right ventricular endocardial stimulation of the heart in complete heart block by means of an intravenous electrode. In 1952 Zoll[10] made use of prolonged rhythmic electrical stimulation of the heart through the intact chest wall in two patients in complete block who had developed prolonged periods of ventricular asystole. One patient survived.

Open heart surgery in its initial stages and the occurrence of complete atrioventricular block following repair of certain intracardiac defects spurred Lillehei and associates, Weirich[11] and Thevenet,[12] in 1958 to demonstrate for the first time that the cardiac rate could be more effectively controlled by electrically stimulating the heart directly from an external power source through a stainless steel wire inserted into the myocardium.

The first successful treatment of complete heart block in man by means of an electrical pacemaker connected to a myocardial electrode took place January 30, 1957, at the University of Minnesota Hospitals.[11] All of these units were primarily unipolar in design, i.e., one stimulating electrode in the myocardium with a second indifferent electrode plate placed subcutaneously. While bipolar electrodes had previously been used, Hunter and Roth[13] in 1959 advocated the use of and designed a bipolar electrode for clinical use, that could be directly inserted into the myocardium.

The Pacemaker

A power source external to the patient was used in all these developments until 1960 when further miniaturization allowed the entire pacemaker (electrodes plus power source) to be totally implanted at operation in a patient. These clinical devices were reported separately by Zoll,[14] Kantrowitz[15] and Chardack.[16]

Although Faraday had described electromagnetic induction in 1831, experiments with living tissue utilizing this method were not carried out for almost 100 years. In 1933 and 1934 Loucke,[17] Light and Chaffee[18] and Fender [19] stimulated nerve tissue by means of buried collodion-coated coils through inductive coupling to a primary coil, while Abrams[20,21] first stimulated the myocardium in 1960 utilizing a similar arrangement.

Newman[22] in 1937, Greig[23] in 1944, Mauro[24] in 1948, Davey[25] in 1949 and Mauro[26] in 1950 all reported on the stimulation of nerve tissue by creating an impulse in a secondarily implanted coil using radio frequency transmission. These experiments culminated in the clinical use of this technique for myocardial stimulation by Glenn[27] (1959) and Widmann[28] (1964). Both inductive coupling and radio frequency transmission, however, necessitated a power source external to the patient. Although this method has been used successfully in patient care, most investigators have continued to utilize units in which the electrodes plus power source could be totally implanted.[29-42]

Although complete heart block, up until quite recently, was considered to be a rather rare clinical condition, we now know quite differently for more than 25,000 patients have been fitted with pacemakers connected to myocardial electrodes since these devices came into clinical use only a few years ago.

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C. Walton Lillehei, M.D.†
New York, New York

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3. Maria and Joseph Gales Ramsay, III, Cardiovascular Research Fund.
4. Sussex County Heart Association, Newton, New Jersey.
5. Anthony Barnett Heart Fund.

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*Present address: 95th Evac. Hosp., Republic of Vietnam, APO, San Francisco, California 96337.

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11-42. May be secured from the author or the reprints.

A Weeping and a Wailing and a Nationalization of Teeth

Oh, to be in England
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Not a farthing needed
For an appendectomy.
Dentures for the asking,
For husband, child, or spouse;
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—Dr. Francis Leo Golden: Jest What the Doctor Ordered.

MINNESOTA STATE MEDICAL ASSOCIATION
116TH ANNUAL MEETING MAY 26•27•28, 1969
CONVENTION HALL, MINNEAPOLIS AUDITORIUM
"THE UPPER-MIDWEST'S GREAT MEDICAL MEETING"

Drastic innovation can best describe the scientific program for the 116th Annual Meeting of the Minnesota State Medical Association May 26, 27 and 28, Convention Hall, Minneapolis Auditorium.

Three exciting days . . . filled with a variety of business, scientific and social events have been arranged by the Committee on Scientific Assembly. President, Doctor O. L. N. Nelson, Minneapolis, is General Chairman of the Committee. Hosts for the 116th Annual Meeting are the members of the Hennepin County Medical Society. Doctor R. E. Anonsen, Minneapolis, President of the Hennepin County Medical Society, is also Chairman of the Committee on Local Arrangements.

A New Approach

Workshop Session '69 is the most recent step taken by the Committee to streamline the scientific program. Featured will be a series of thirty-two workshops, each one hour in length. Each workshop will be given twice, giving physicians the opportunity to attend a maximum number of presentations. Speakers for the workshop sessions have been selected from the ranks of eminent Minnesota specialists and consultants, who will discuss every-day problems encountered by the practicing physician. Each workshop session is limited to 20 physicians, and therefore pre-registration is encouraged by the Committee.

The Workshop '69 schedule is as follows:

MONDAY, MAY 26
IDENTICAL WORKSHOP SESSIONS
2:00-3:00 P.M. & 3:45-4:45 P.M.

What To Do Until The Psychiatrist Comes	T. P. Burton
Anesthesia and Pulmonary Disease	H. D. Westgate
Drugs For Nervousness?	B. C. Schiele
Preventing Complications of Acute Meningitis	M. R. Gomez
Current Status Of Organ Transplantation	J. S. Najarian
Hemorrhoids—To Operate Or Not To Operate That May Be The Question	C. E. Culp
Cutaneous Patterns Of Fatal Disease	R. K. Winkelmann
Hand Injuries—13 Things To Avoid	K. H. Sponsel
Thyroid Function Testing—An Exercise In Medical Detection	C. A. Gorman
Burns—How To Treat Them	J. W. LaFave
Multiple Injuries	J. F. Perry, Jr. Donald L. Erickson, Paul Arnesen, Josiah Fuller, Harrison Farley

TUESDAY, MAY 27
IDENTICAL WORKSHOP SESSIONS
2:00-3:00 P.M. & 3:45-4:45 P.M.

Children Who Don't Grow	A. B. Hayles
Anesthesia And Patient Monitoring	J. J. Buckley
Thyroid Disease—A Therapeutic Controversy	A. L. Schultz F. C. Goetz F. R. Keating O. H. Beahrs A. J. Kremen

Clotters And Bleeders	J. R. Edson
Belchers And Bloaters	W. L. Blackwood, M. D. Levitt
Chest Injuries	R. E. Larson, J. A. Culligan Josiah Fuller
Reflux And The Assaulted Kidney	G. W. Koos
Menopause—An Organic vs. A Psychiatric Problem?	B. F. P. Williams
Rheumatism And Drugs	P. H. Andreini
The Threatening Eye	W. J. Slack
CCU ECG Group Problem Solving Sessions	Gerald B. Lee, John W. LaBree

WEDNESDAY, MAY 28
IDENTICAL WORKSHOP SESSIONS
9:30-10:30 A.M. & 11:00-12:00 Noon

Prevention Of Rh Disease	H. F. Polesky, E. B. Berglund, A. R. Thelemann
Anesthesia In The Office And Emergency Room	J. W. Smith
Computer Applications In Medical Practice	J. A. Hilger
Fertility And Infertility	John Sciarra
Abdominal Pain	L. J. Hay
Practical Management Of Acute Head Injuries	R. F. Galbraith, E. S. Wisiol
Nonsuture Technique In Surgical Treatment Of Varicose Veins	D. A. Felder
The New Diuretics	D. A. Duncan, Ross M. Tucker
Pulmonary Insufficiency	W. A. Corson, R. V. Ebert
Saving The Cold and Pulseless Limb	Yoshio Sako, C. W. Manz

"In Depth" Treatment

The success of the "in depth" sessions initiated at the 1968 meeting has given impetus to a similar series at the 1969 meeting. The first of two "in depth" sessions will be held Monday, May 26, 9:30 A.M. to 12:00 P.M. Doctor William E. Segar will be in charge of the session titled "Fluids and Electrolytes—How Much, What Kind and When." "Cancer Chemotherapy" will be treated "in depth" Tuesday, May 27, at 9:30 A.M. Chairman for this session is Doctor David Ahmann. Topics and participants in the Chemotherapy session are:

The Chemotherapy Of Solid Tumors In Children	Loren N. Vorlicky
The Chemotherapy Of Gastrointestinal Cancer	Irving J. Lerner
Progress In The Management Of The Patient With Lymphoma	John H. Brown
Current Thoughts About The Chemotherapy Of Leukemia	Joseph M. Kiely
Testicular Cancer—Current Chemotherapy	John F. Foley Omaha, Neb.
The Medical Management Of Disseminated Breast Cancer	David L. Ahmann

The program is acceptable for 14 prescribed hours by the American Academy of General Practice.

Noon Luncheons Feature Popular Topics

Two luncheon meetings scheduled for Monday and Tuesday mark another departure from the traditional round table luncheons of past years.

On Monday, May 26, 12:15 P.M., Doctor Arthur C. Aufderheide, Duluth, will speak on the topic "To the North Pole by Snowmobile." The Tuesday luncheon speaker will be the Reverend Philip Hansen, White Bear Lake. Reverend Hansen is Chairman of the Minnesota Commission on Alcohol Problems, and will speak on the topic of "Alcoholism."

Business Sessions

The House of Delegates meeting and Reference Committee meetings will highlight the business session of the 116th Annual Meeting. The House will convene Sunday, May 25, 2:00 P.M., Holiday Inn Central, and will reconvene

Tuesday, May 27, 7:00 P.M. Reference Committees will meet Sunday at 8:00 P.M. The Annual Banquet will be held Monday, May 26, 7:00 P.M. This marks another change from the traditional Tuesday date. The banquet will be preceded by a social hour beginning at 6:00 P.M. Dancing and a late evening buffet will climax the banquet program. Fifty Club candidates will be honored guests at the banquet.

The Distinguished Service Medal will be awarded and a medal for the outstanding scientific exhibit will be presented by the Southern Minnesota Medical Association.

The Delegates, New Members, Officers and Sportsmen's dinner will be held Sunday, May 25, 6:00 P.M. at the Holiday Inn Central.

Sports Events

The annual golf tournament will be held at the Midland Hills Country Club, St. Paul. Tee off time is 9:00 A.M., Sunday, May 25. Early tee times are recommended. Prizes will be awarded. The green fee is $15.00. Skeet and trap events, including razzle dazzle, are scheduled Sunday, May 25, from 10:00 A.M. to 4:00 P.M. at the Minneapolis Gun Club. Prizes will be awarded. Participants in sports events and their wives are invited to attend as guests of the Minnesota State Medical Association, the Delegates, New Members, Officers and Sportsmen's dinner on Sunday. An annual bridge tournament is also scheduled for Sunday night at 8:00 P.M.

Pre-registration Desirable

Physicians are encouraged to pre-register by completing the registration card enclosed with current issues of the Newspage and the official Annual Meeting program mailed to all members. By completing and returning this card by May 5 to the State Office physicians can be certain that their badges will be waiting for them at the advance registration desk in the Minneapolis Auditorium Convention Hall.

Time Table

MONDAY, MAY 26

A.M.	Visit scientific and technical exhibits
9:30 A.M. to 12:00 P.M.	"FLUIDS AND ELECTROLYTES—HOW MUCH, WHAT KIND AND WHEN" William E. Segar
(Intermission: 10:30 A.M.-11:00 A.M. Visit scientific and technical exhibits)	
12:15 P.M.	LUNCHEON—"TO THE NORTH POLE BY SNOWMOBILE" Arthur C. Aufderheide
1:30 P.M.	Visit scientific and technical exhibits
2:00 P.M. to 3:00 P.M. Repeated: 3:45 P.M. to 4:45 P.M.	WORKSHOPS
7:00 P.M.	ANNUAL BANQUET Reception at 6:00 P.M. Presentations and Entertainment Dancing and Late Evening Buffet

TUESDAY, MAY 27

A.M. Visit scientific and technical exhibits
9:30 A.M. to 12:00 P.M. "CANCER CHEMOTHERAPY"
Chairman—David L. Ahmann

THE CHEMOTHERAPY OF SOLID TUMORS IN CHILDREN
Loren N. Vorlicky

THE CHEMOTHERAPY OF GASTROINTESTINAL CANCER
Irving J. Lerner

PROGRESS IN THE MANAGEMENT OF THE PATIENT WITH LYMPHOMA
John H. Brown

CURRENT THOUGHTS ABOUT THE CHEMOTHERAPY OF LEUKEMIA
Joseph M. Kiely

(Intermission: 10:30 A.M.-11:00 A.M.
Visit scientific and technical exhibits)

TESTICULAR CANCER—CURRENT CHEMOTHERAPY
John F. Foley

THE MEDICAL MANAGEMENT OF DISSEMINATED BREAST CANCER
David L. Ahmann

Questions and discussion by the participants

12:15 P.M. LUNCHEON—"ALCOHOLISM"
Reverend Philip Hansen, White Bear Lake
1:30 P.M. Visit scientific and technical exhibits
2:00 P.M. to 3:00 P.M. WORKSHOPS
Repeated: 3.45 P.M. to 4.45 P.M.

WEDNESDAY, MAY 28

A.M. Visit scientific and technical exhibits
9:30 A.M. to 10:30 A.M. WORKSHOPS

(Intermission: 10:30 A.M.-11:00 A.M.
Visit scientific and technical exhibits)

Repeated: 11:00 A.M. to 12:00 P.M.

EXHIBITS

Because most of the Annual Meeting activities will be held in the Minneapolis Auditorium Convention Hall, physicians will have more time to visit the many excellent scientific and technical booths. All physicians attending the meeting are invited to visit the technical exhibits and extend their appreciation to the representatives of the firms who have participated in this meeting, thus insuring future meetings for our Association.

The Woman's Auxiliary will meet in conjunction with the Annual Meeting of the Minnesota State Medical Association.

Meetings and Announcements

We live and learn, but not the wiser grow.—John Pomfret

MAY

Minnesota State Medical Association
116th Annual Meeting, Convention Hall, Minneapolis, May 26, 27, 28.

Hennepin County Medical Society
Regular Meeting, Pick-Nicollet Hotel, Minneapolis, 6 P.M., May 5.

Scott-Carver County Medical Society
Regular Meeting, Wagner's Supper Club, Jordan, 6:30 P.M., May 6.

Zumbro Valley Medical Society
Regular Meeting, Mann Hall, 7 P.M., May 7.

Minnesota Academy of Medicine
Town & Country Club, St. Paul, 6 P.M., May 14.

Stearns-Benton County Medical Society
Regular Meeting—St. Cloud Veterans Hospital, 6:30 P.M., May 15.

McLeod County Medical Society
Regular Meeting, 6:30 P.M., May 15, Location to be announced.

Steele County Medical Society
Inn Towne Motel, Owatonna, 6:30 P.M., May 20.

Blue Earth Valley Medical Society
Regular Meeting, Interlaken Golf Club, 7 P.M., May 21.

Waseca County Medical Society
Regular Meeting, Waseca Memorial Hospital, 6:30 P.M., May 26.

Blue Earth County Medical Society
Mankato Golf Club, 7 P.M., May 26.

Range Medical Society
Executive & General Meeting, 7:15 P.M., Dinner—Location to be announced, May 27.

Minnesota Academy of Ophthalmology & Otolaryngology
Regular meeting to coincide with time and place of Minnesota State Medical Association annual meeting.

Courses at the University of Minnesota

New Knowledge in the Diagnosis and Treatment of Rheumatic Diseases

This course is planned for May 9 and 10, and is directed toward the practicing physicians with emphasis on this newer information and its application to the rheumatic problems encountered in every medical practice. Ample time has been left for discussion after each presentation so participants will have the chance to have their questions answered.

The course has been planned by Doctors John G. Mayne and John W. Worthington, Mayo Graduate School of Medicine, and is co-sponsored by the Committee on Rheumatology and Rheumatic Diseases of the Minnesota State Medical Association, and by the Minnesota Chapter of the Arthritis Foundation. The course is offered by the Office of Postgraduate Educational Activities of the College of Medical Sciences, and conducted by the Department of Conferences and Institutes, General Extension Division, University of Minnesota. Tuition is $25.00. Approved A.A.G.P. hours: 11 hours.

Gastro-Intestinal Surgery

The University of Minnesota will present a course on Gastro-Intestinal Surgery on May 21-24, 1969.

Anesthesiology

The University of Minnesota will present a Continuation Course in Anesthesiology May 5-7, 1969. The theme of this year's course is *Do the Patient No Harm.*

For further information concerning all of the above courses contact: Lee D. Stauffer, College of Medical Sciences, Box 193 Mayo Building, University of Minnesota, Minneapolis 55455.

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Take particular care in cirrhosis or severe ischemic heart disease and in patients receiving corticosteroids, ACTH, or digitalis. Severe salt restriction is not recommended. Use cautiously in patients with ulcerative colitis or gallstones (biliary colic may be precipitated). Bronchial asthma may occur in susceptible patients.
Adverse Reactions: The drug is generally well tolerated. The most frequent side effects are nausea, gastric irritation, vomiting, diarrhea, constipation, muscle cramps, headache, dizziness and acute gout. Other potential side effects include angina pectoris, anxiety, depression, bradycardia and ectopic cardiac rhythms (especially when used with digitalis), drowsiness, dull sensorium, hyperglycemia and glycosuria, hyperuricemia, lassitude, restlessness, transient myopia, impotence or dysuria, orthostatic hypotension which may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics, leukopenia, aplastic anemia, skin rashes, thrombocytopenia, agranulocytosis, nasal stuffiness, increased gastric secretions, nightmare, purpura, urticaria, ecchymosis, weakness, uveitis, optic atrophy and glaucoma, and pruritus. Eruptions and/or flushing of the skin, a reversible paralysis agitans-like syndrome, blurred vision, conjunctival injection, increased susceptibility to colds, dyspnea, weight gain, decreased libido, dryness of the mouth, deafness, anorexia, and pancreatitis when epigastric pain or unexplained G.I. symptoms develop after prolonged administration. Jaundice, xanthopsia, paresthesia, photosensitization and necrotizing angiitis are possible.
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GENERAL SURGEON: Board certified or eligible. 269 bed General Medical and Surgical Hospital in Michigan's Upper Peninsula. Licensure any state, salary dependent upon background and qualifications. Excellent benefits for retirement, vacations, sick leave, and professional improvements. Non-discrimination in employment. Contact Chief of Staff, VA Hospital, Iron Mountain, Michigan 49801.

WANTED: G.P. for one year Locum Tenens or permanent practice in a friendly, relaxed, medically progressive community in northern Minnesota. Summer and winter recreation excellent; liberal salary & ample time off. Early partnership if desired. Start July 1, 1969 or sooner if desired. Contact Doctors Brende and McQuoid, Littlefork, Minn. 56653 or call collect 218-278-6651.

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INTERNIST: Board certified or eligible. 269-bed General Medical and Surgical Hospital in Michigan's Upper Peninsula. Licensure any state, salary dependent upon background and qualifications. Excellent benefits for retirement, vacations, sick leave, and professional improvements. Non-discrimination in employment. Contact Chief of Staff, VA Hospital, Iron Mountain, Michigan 49801.

THREE MAN group in North West Wisconsin Resort, State Conservation and Retirement Area needs two more physicians adequately to serve their practice. Facilities offered are three-room physician suites, X-ray and lab under AMT technician, RN-only nursing personnel. New accredited thirty-two bed hospital and forty-six bed nursing home. Deer and duck hunting, fishing within five minutes of town. Internist most needed; generalists welcomed. Will meet any reasonable salary request. Partnership after one year. Write: MINNESOTA MEDICINE—365; 375 Jackson St., St. Paul 55101.

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WANTED: General practitioner to join two young general practitioners in well-established practice in suburban St. Paul. Excellent office space with lab, x-ray, and emergency room. Salary negotiable, with an association leading to early partnership opportunity. Write MINNESOTA MEDICINE 412, 375 Jackson St., St. Paul 55101.

INTERNIST AND GENERAL PRACTITIONER wanted to join a five-man clinic group in Minneapolis. Complete laboratory and X-ray with board roentgenologist. Excellent hospital staff associations. Salary arrangement to start with, early partnership. Write MINNESOTA MEDICINE—289; 375 Jackson, St. Paul, 55101.

CANOE TRIPS—Complete relaxation in the Quetico-Superior Wilderness. Cruise, fish and explore, or base camp on remote lakes. Paddle, motor or fly in. Bring your family—return home completely rested. Cost only $9.00 per diem, $7.00 under 12. Write: Bill Rom, Dept. MM, Canoe Country Outfitters, Ely, Minnesota.

BENSON & ASSOCIATES: Business & Professional Collection Specialists. No charge if no collection made. Ph.: 888-2242, 8601 Nicollet Ave., Bloomington, Minn.

INTERNIST—Certified, FACP, endoscopial, available June 1969. Write: Minnesota Medicine-425, 375 Jackson St., St. Paul 55101.

GENERAL PRACTITIONER urgently needed with two man partnership in Northern Minnesota County Seat Community has modern accredited hospital, stable industry, fine schools and excellent hunting and fishing. Contact Administrator, Roseau Area Hospital, Roseau, Minnesota. Telephone No. 218-463-2500.

EXCELLENT OPPORTUNITY for one or two general practitioners. Deer River, Minnesota will be needing one or possibly two physicians by June 1, 1969. The present partnership has an extremely busy practice with higher than average income. An equipped ten room clinic in the hospital is available. For further information contact David McClure, Administrator, Community Memorial, Deer River, Minn. Call collect (218)-246-8245 weekdays or 246-8274 evenings or weekends.

WANTED: Young General Practitioner to join 5 man general practice group. Services of General Surgeon and Radiologist immediately available. College town serving population of 22,000, 30 miles from Twin Cities. Contact Roland M. Hammer, M.D., River Falls Medical Clinic, River Falls, Wisconsin. Phone 425-5322.

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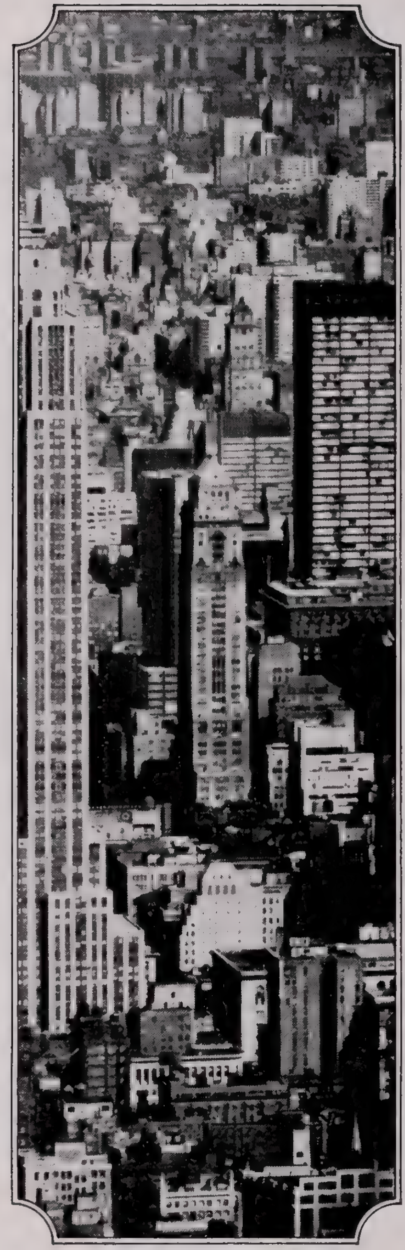

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Continued from page 883

WANTED: G.P. to join clinic serving population area of 12,000. City has new hospital, new clinic building, two nursing homes, new Jr-Sr high school, new swimming pool, rich farming area. Fishing and hunting nearby; metropolitan city close by. Salary open and partnership if interested. Write Minnesota Medicine-423; 375 Jackson, St. Paul 55101.

GENERAL PRACTITIONER WANTED to join well-established three man group in Twin City area. Starting salary $20,000.00 to $25,000.00 range with opportunity for early partnership; or, will negotiate. Write: Minnesota Medicine-424, 375 Jackson, St. Paul 55101.

TEN MAN MULTISPECIALTY group needs an ophthalmologist and another pediatrician. New clinic building, complete laboratory and x-ray facilities. 180 bed modern hospital across street from clinic. Early share-holder status. Salary open. Write or call the Lenont-Peterson Clinic, Ltd., C. A. Tietz, M.D., area code 218, 741-4292, Virginia, Minnesota 55792.

WANTED: Young physician for association leading to partnership with four well established General Practitioners in fast growing suburb of St. Paul. Excellent clinic facilities in nearly new, partnership owned, well equipped, medical center building. Write: Minnesota Medicine-421, 375 Jackson, St. Paul 55101.

WANTED. General practitioner wanted to join three-man group in a fast-growing area just 30 minutes south of the Twin Cities. You will practice in a new clinic, hospital and nursing home. A complete resume of facilities, practice and area is available. Contact M. H. Hunter, M.D., River's Edge Medical Clinic, Farmington, Minnesota. Telephone 612-463-7181.

OXBORO MEDICAL CLINIC BUILDING (only) for sale in Bloomington, Minnesota's third largest city. Earn attractive return while current lease expires in four years. Clinic comfortably houses 11 doctors, each with 3½ examination rooms. Central air conditioning, adequate parking, and much more. Contact Towle Real Estate Co., 333-2445, Area Code 612. James R. Bingham.

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ASSOCIATE-GENERAL PRACTICE—Excellent financial opportunity. Large medical-surgical practice, Northern Wisconsin in vacation-farming area 75 miles from the Twin Cities. Modern clinic adjacent to 84 bed JCHA hospital complex. Salary open. Partnership available. Write: MINNESOTA MEDICINE—428. 375 Jackson St., St. Paul 55101.

INTERNIST—Six physicians in corporate practice wish to increase service to area by adding general internist to its staff. Fringe benefits are available. Salary open. 150 bed open staff joint commission accredited hospital in community. Write: MINNESOTA MEDIINE—429, 375 Jackson St., St. Paul 55101.

MINNESOTA PROFESSIONAL CORPORATION with fringe benefits wishes to add a general practitioner. Full rights and privileges after one year. Joint commission accredited hospital, open staff. Write: MINNESOTA MEDICINE—430, 375 Jackson St., St. Paul 55101.

GENERAL PRACTITIONER wanted for 4 man GP group with board surgeon associated with community sponsored prepayment plan in NE Minnesota area of 14,000 located on Lake Superior near Duluth; accredited hospital with radiologist, pathologist and internist services next door to modern clinic; good schools with swimming pool and indoor ice arena, golf, hunting, fishing; liberal salary, $20,000-$25,000 first year; full partnership 6 months; equitable rotating call schedule. No age limit. Write Medical Director, Community Clinic, Two Harbors, Minnesota.

PSYCHIATRIC RESIDENCIES: We offer nothing but excellent psychiatric training in a stimulating, well organized program located in a culturally advantaged community. Approved psychiatric training. Traverse City State Hospital, Michigan Department of Mental Health. Three and five year programs. Salary, 3 year program: $10,669; $11,191; $12,131. 5 year program: $12,152; $14,031; $16,328. $21,944; $23,093. NIMH-GP stipends available. Located in Michigan's serene, scenic recreation area on Grand Traverse Bay. Contact Dr. Paul E. Kauffman, Director of Training, Traverse City State Hospital, Traverse City, Michigan 49684. An equal opportunity employer.

Science

A contemporary historian, speaking of our scientific advances, expresses the choice before us: "If things go well, the epitaph of history may run: 'Here lie the technicians, who united mankind.' And if things go badly: 'Here lie the technicians, who exterminated the human race.' "—Christian Century

Dial Access Information for Physicians

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#262: *Spinal Cord Tumors*
#263: *Buccal Smear, Indications for*
#264: *Diarrhea With Vomiting in Infants, Home Management of*
#265: *Management of Stasis Dermatitis*
#266: *Recognition and Management of Cutaneous Drug Reactions*
#267: *Indications for Gastroscopy and Gastrophotography*
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#269: *Acute Diagnosis and Management of Pancreatitis*
#270: *Chronic Diagnosis and Management of Pancreatitis*
#271: *Barium Enema After Age 40*
#272: *Occult Hydrocephalus*
#273: *The Diagnosis of PKU*
#274: *Suicide Attempts with Sedative Drugs*
#275: *Frostbite: Treatment Today*
#276: *Chemoprophylaxis for Tuberculosis*
#277: *Anemia of Leukemia, Management of*
#278: *Myocardial Infarction—Sexual Intercourse After*
#279: *Exercise and Coronary Heart Disease*

For description of tapes, see hospital bulletin board or write:

L. G. Berglund
Dial Access Project Director
Northlands Regional Medical Program
375 Jackson Street
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Minnesota Medicine at a Glance

Post-Intubation Granuloma of Larynx—*Schlorf and Duvall* Page 717

The large number of operations currently being performed via endotracheal anesthesia demands that all concerned be aware of the complication of post-intubation granuloma of the larynx. It should be suspected, and treated, whenever a patient becomes hoarse or develops ear pain or a persistent cough, several weeks after a translaryngeal intubation. The lesion is pathologically a pyogenic granuloma, results from trauma to the larynx and has a characteristic laryngoscopic appearance. It often responds to a medical regimen, but in problem cases surgical removal is indicated.

Hepatitis in Infectious Mononucleosis—*Kitzmiller* Page 721

Eighteen cases of syncope on coughing have been diagnosed at the Mayo Clinic in the last eighteen years. The typical patient is a heavy user of alcohol and a heavy smoker, and is obese, with clinical or laboratory evidence of obstructive lung disease. Therapy primarily is correction of bad habits.

Vaginal Hormonal Cytology—*Litwak and Mussey* Page 731

The value of exfoliative cytology of vaginal cells in interpreting the constant interplay of hormones should come under close scrutiny. Physicians concerned with vaginal cytology should find this article helpful in defining basic indices. The normal vaginal smear is described as well as smears associated with the period before and after ovulation. Several clinical syndromes with a characteristic vaginal cytology are described: among them, ovarian decline, estrogen therapy, and threatened abortion. The use of hormonal cytologic studies in children is briefly described. The hormonal colpocytologic procedure appears to add a significant increment to the physician's judgment.

Toxoplasmosis and Pneumocystis Carinii Pneumonitis—*Theologides et al.* Page 737

A case of seminoma of the left testis, treated with radiation therapy and followed by chronic lymphatic leukemia, is described in detail. The patient was treated with radiation and androgen steroids. He died of a combined infection with pneumocystis carinii and toxoplasmosis. The authors urge early diagnosis, since therapy may be life-saving.

Treatment of Myocardial Infarction—*Trajano et al.* Page 743

The coronary care unit at Mount Sinai Hospital in Minneapolis reports on 100 acute myocardial infarctions with a hospital mortality of 21 percent. The authors estimate the treatment in the Coronary Care Unit reduced the mortality 11 to 13 percent. The reduction was effected by more favorable results in arrhythmias.

Drug Fever Due to Procainamide—*Pierach* Page 813

A 64-year-old male patient demonstrated drug fever due to procainamide. Fever started sixteen days after commencement of Pronestyl® therapy, 250 mg., four times daily, by mouth. The day after discontinuance the temperature dropped to normal, but later rose briefly again after a single provocative dose of 250 mg.

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(1) Siver, R. H.: CMD, *21*:109, September 1954. (2) Frykman, H. H.: Minn. Med., *38*:19-27, January 1955. (3) McGivney, J.: Tex. State Jour. Med., *51*:16-18, January 1955. (4) Quehl, T. M.: Jour. of Florida Acad. Gen. Prac., *15*:15-16, October 1965. (5) Weekes, D. J.: N.Y. State Jour. Med., *58*:2672-2673, August 1958. (6) Weekes, D. J.: EENT Digest, *25*:47-59, December 1963. (7) Abbott, P. L.: Jour. Oral Surg., Anes., & Hosp. Dental Serv., 310-312, July 1961. (8) Rapoport, L. and Levine, W. I.: Oral Surg., Oral Med. & Oral Path., *20*:591-593, November 1965.

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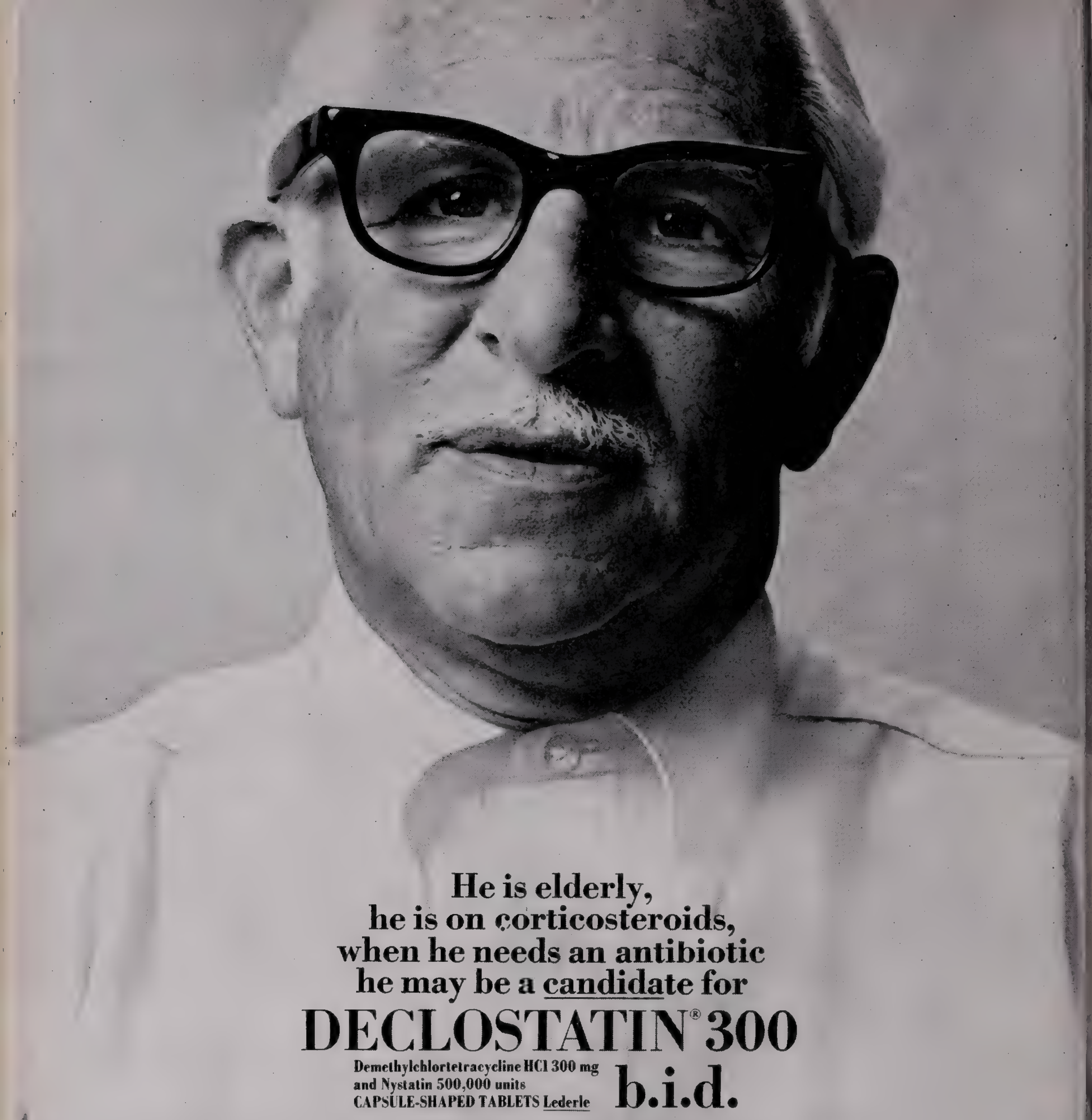

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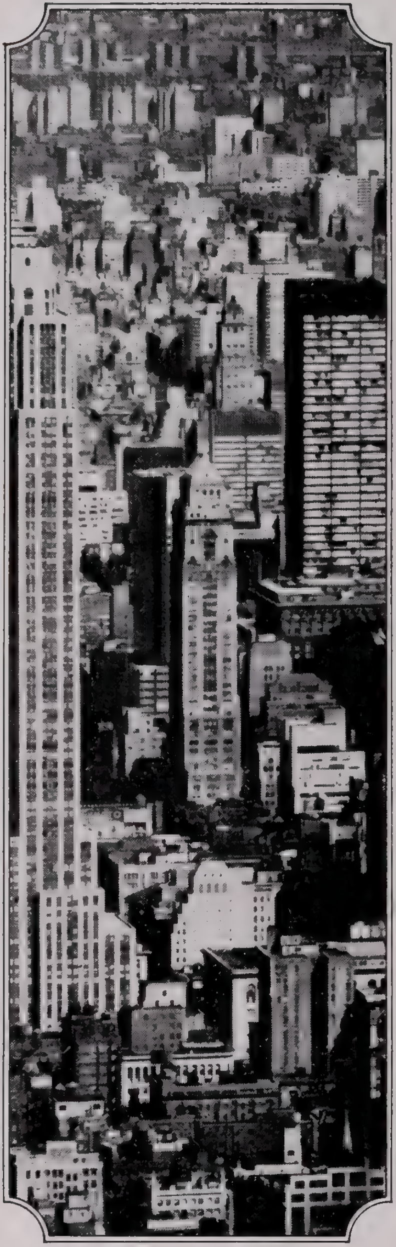

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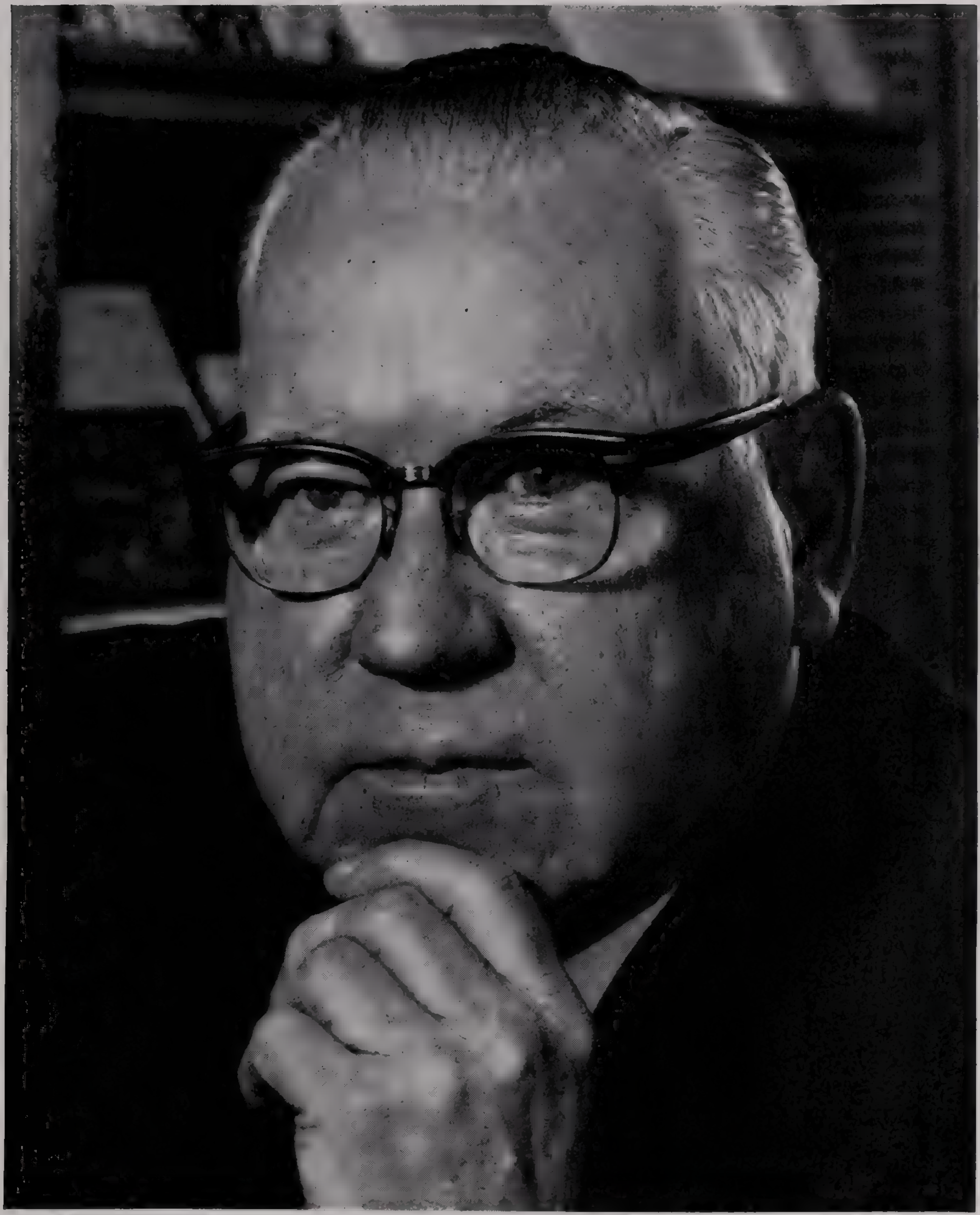

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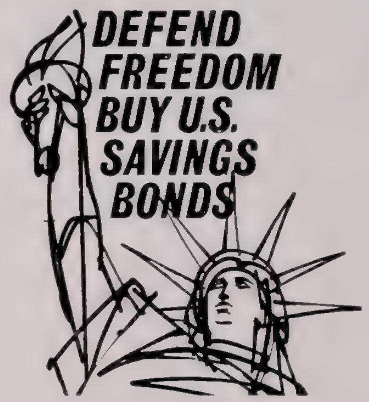
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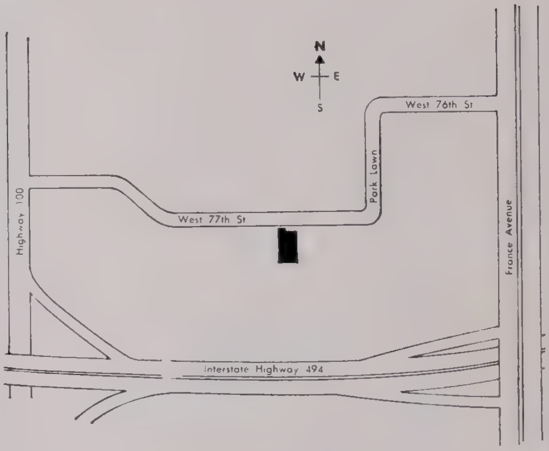
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President's Letter

As I begin this first letter as your President, I am reminded that we have just observed our 116th Anniversary in May. It was in 1853 that doctors in Minnesota found it necessary and beneficial for the practice of medicine to join together and organize the Minnesota State Medical Association and its component societies. Great credit must be given to all of the members, the various committees and their chairmen, the Council and the officers and all the members of the Houses of Delegates who have worked so diligently and have given so largely of their time to the betterment of our Association over these many years. We must pay homage to them all.

It is disturbing, however, that all doctors in Minnesota have not been members of organized medicine. In 1968 there were 4,989 licensed physicians in Minnesota. Of these, there were 3,375 active members and 423 residency members of the Minnesota State Medical Association and 3,208 active members and 413 residency members of the American Medical Association.

It is human nature, of course, that all people including doctors do not join organizations, or do not agree with policies of organizations. However, it is rather difficult to understand why one who spends so many years in training as does the doctor of medicine is willing to forfeit his right to speak out and be really heard of effectively either by the profession or by the general public.

The doctor who is not a member of his local county or district society, who is not a member of the Minnesota State Medical Association and who is not a member of the American Medical Association has no real voice, though he may be critical of both, in determining the policies of organized medicine or the destiny of the practice of medicine. The Academy of General Practice working together with State Medical Associations and the American Medical Association has brought the General Practitioner back from the brink of no return to a respected and valued position in the Family Practice of Medicine. Likewise, in the years past, the American College of Surgeons pioneered the raising of the standard of surgical practice in hospitals and were able to succeed because of organization.

I therefore ask all members of our Association to make a determined effort to encourage all our brethren to join with us in this great profession we must all strive to improve.

June, 1969

Delmar R. Gillespie

Delmar R. Gillespie, M.D.,
President
Minnesota State Medical Association

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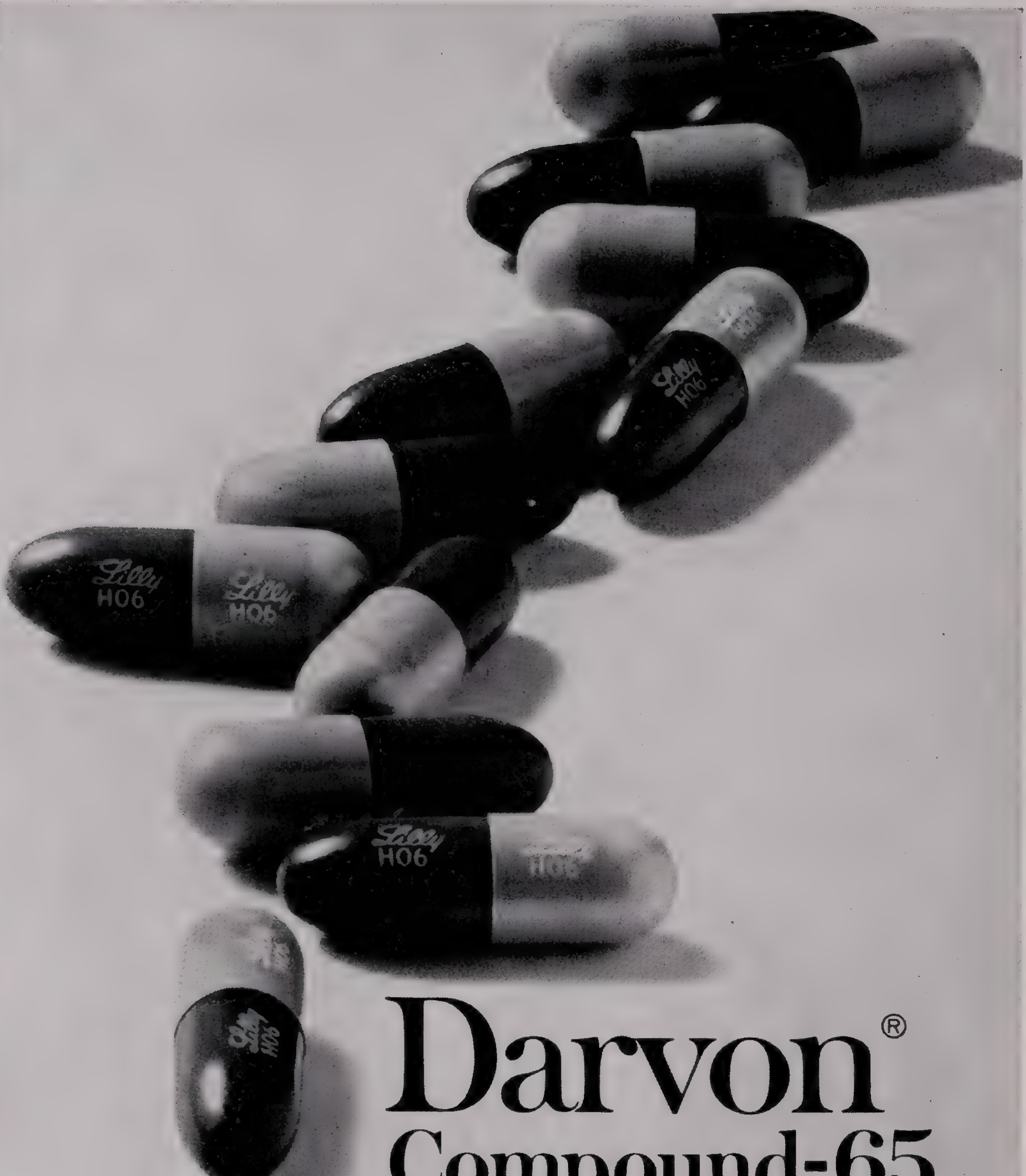
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Thioflavine - T

in Basal Cell Carcinoma and Ameloblastoma

WILLARD C. PETERSON, JR., M.D.[*]
ROBERT J. GORLIN, D.D.S.[†]
Minneapolis, Minnesota

In a previous paper, the histologic similarities between basal cell carcinoma and ameloblastoma[‡] were discussed.[1] If one considers the similar origins of skin appendages and the dental apparatus it is not surprising that a histologic similarity may exist between these two tumors.

Between the fifth and seventh week of fetal life both cutaneous and oral ectoderma undergo proliferation; the epidermis becomes double layered, and during the third month *in utero* primary epithelial germs proliferate and reticulum fibers appear in the dermis. Almost analogous changes are taking place orally; at about the sixth intrauterine week, epithelium covering the jaw proliferates at 20 different points corresponding to the future position of the deciduous teeth.

Basal cell carcinoma has been shown to have thioflavine-T reactivity in a certain percentage of specimens studied with this staining method.[2] Because of the histologic similarity between basal cell carcinoma and ameloblastoma, 24 basal cell carcinomas and 12 ameloblastomas were compared on the basis of the thioflavine-T staining technique.

Material and Methods

Sections from 24 formalin-fixed, paraffin-embedded specimens of basal cell carcinoma and 12 specimens of ameloblastoma were stained with hematoxylin and eosin for microscopic comparison. These same tumors were then examined for thioflavine-T reactivity using the method of Hobbs and Morgan.[3] The sections were examined under a microscope (Leitz Ortholux) employing a mercury light source (HBO-200 Osram), using a special cemented barrier filter, UV filter 3mm BG12, and heat absorbing filters (2mm KGI and 4mm BG38). The fluorescence of thioflavine-T was yellowish green. Positive amyloid controls were used with the foregoing technique.

Results

In both series (Table) somewhat over one half of the sections exhibited positive fluorescence with the thioflavine-T method. No definite patterns of fluorescence were observed in either basal cell carcinoma or ameloblastoma. In many of the tumors of both types, fluorescence appeared only in the interstitial areas outlining the individual cells clearly; however, in other sections the fluorescence appeared not only in the interstitial areas but also in many of the tumor cells, giving the appearance of somewhat large homogeneous areas of fluorescence. In basal cell carcinoma, surface keratin as well as keratin within hair follicles fluoresced with this technique. This was, of course, easily identifiable by structure and did not cause confusion.

---

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[‡] See Test Your Word Score Page 933.

TABLE
Thioflavine—T Reactivity

	Ameloblastoma	Basal Cell Carcinoma
Positive	7	14
Negative	5	10
Total	12	24

Comment

The histologic similarity of basal cell carcinoma and ameloblastoma is considerable (Figures 1 and 2). The question of origin of the basal cell epithelioma is not as yet clearly defined. It occurs almost exclusively on the hair-bearing areas of the body, the face being the most common site of origin. This tumor has been known to metastasize;[4,5] however, this is not a common event. Instead, the tumor tends to invade locally. Histologically, basal cell carcinoma can be divided into differentiated and undifferentiated forms. When differentiation occurs, it is in the direction of hair, sebaceous and apocrine glands. The tumor has a characteristic cell which exhibits a large, oval, deeply basophilic nucleus. The cytoplasm, as a rule, is scanty with an indistinct cytoplasmic membrane.

Ameloblastoma is a tumor of slow growth. It may have its origin in the epithelial lining of a dentigerous cyst, the basal layer of the oral mucous membrane or the epithelial remnants of the enamel organ. Ameloblastoma occurs most frequently in the molar-ramus region of the mandible. It is locally invasive and has a marked tendency to recur following conservative removal. It has also been known to metastasize, but this is a rare event.[6] Microscopically, basophilic epithelial cells are seen grouped in nests and cords within the collagenic fibrous connective tissue stroma. The peripheral cells are cuboidal to columnar in nature; and in the central, loose, stellate reticulum-like area, they exhibit a tendency to differentiation into squamous-like cells (acanthomatous ameloblastoma).

Conclusions

Both basal cell carcinoma and ameloblastoma show certain similarities. In both, the origin is from primordial epithelium; both show a tendency to be locally invasive and to recur if not adequately removed. Both have been reported to metastasize occasionally. Microscopically each is composed of islands of epithelial cells in a similar connective tissue stroma which shows separation or clefting away from the tumor mass. In both, the epithelial cells show polarization away from the border of the tumor. In view of these similarities it is not surprising that ameloblastoma, like basal cell

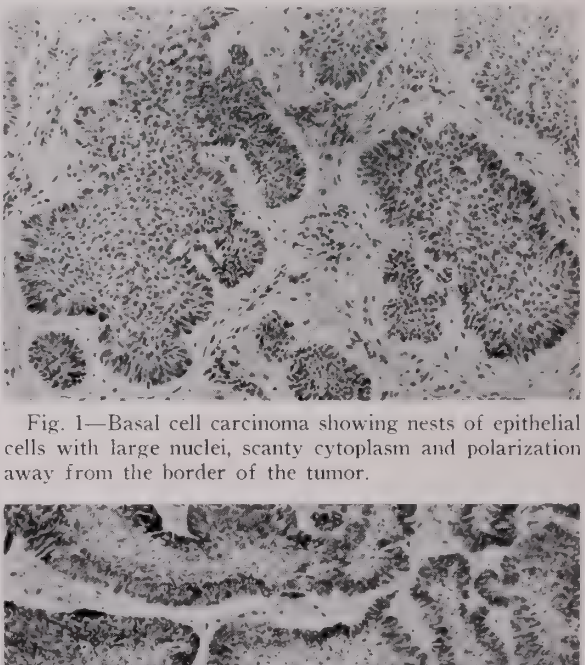

Fig. 1—Basal cell carcinoma showing nests of epithelial cells with large nuclei, scanty cytoplasm and polarization away from the border of the tumor.

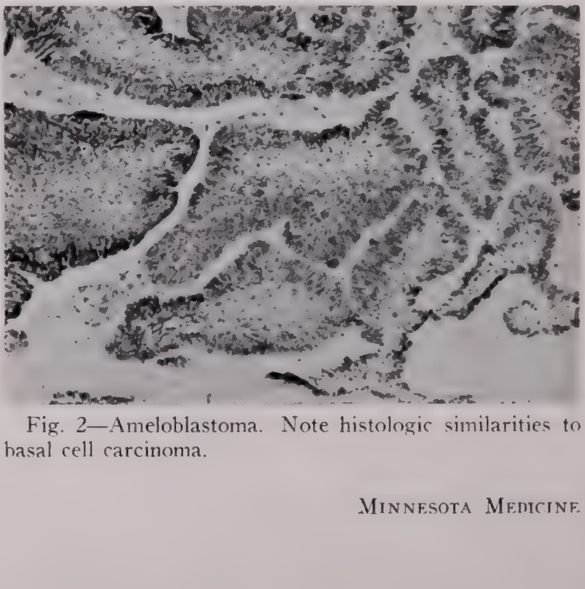

Fig. 2—Ameloblastoma. Note histologic similarities to basal cell carcinoma.

carcinoma, should show considerable thioflavine-T reactivity within the tumor mass. This thioflavine-T reactivity or fluorescence shows no particular pattern in either tumor, occurring both within tumor cells and in the adjacent connective tissue stroma.

The thioflavine-T technique is considered superior in the demonstration of amyloid. It is more sensitive than congo red or methyl violet. However, it is important to emphasize that this technique is not diagnostic for the presence of amyloid. Other substances will show thioflavine-T positivity, such as fibrous proteins, mucopolysaccarides, and mucoproteins. Therefore the finding of thioflavine-T positivity in these tumors in no way identifies the substance as amyloid; it may be merely an amyloid-like mucopolysaccaride or mucoprotein.

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School of Salernum

Now if perhaps some have desire to know,
The number of our bones, our teeth, our veines,
This verse ensuing plainly doth it show,
To him that doth observe, it taketh paines:
The teeth thrise ten, and two, twise eight arow.
Elev'nscore bones save one in us remaines:
For veines, that all may vaine in us appeare,
A veine we have for each day in the yeare:
All these are like in number and connexion.
The difference growes in bigness and complexion.

—Regimen Sanitatis Salerni

Editor's note: The School here asserts that we humans are all anatomically alike, with 32 teeth, 219 bones, and 365 veins. We differ only in size and color. This must have been the origin of our more modern memory devices: "On old Olympus tip top a fat . . ." for the cranial nerves; and "Never lower Tillie's . . ." for the bones of the wrist; and "As she lay extended Sir Oliver . . ." for branches of the carotid artery. I am sure you all recall them.

Sympathy

Fashionable New Yorkers in the seventeenth century felt obliged to maintain their prestige, when sick in bed, not only by calling a physician but also by employing the services of two "comforters" whose incredible occupation was to comfort the patient throughout the long hours of the night. Dressed in black and having a funereal expression, these cheerful chaps sang mournful hymns, read sad parts of the Bible, and discussed death and the Hereafter. By dawn, the patient was usually hoping for the worst.

—Freling Foster, Collier's

The Skin Moves

In spite of his young age a twenty-year-old railway worker was stricken with an ailment oftener met in older men. It was a varicose vein of the hip. The youth was brought to the clinic with complications caused by an operation he had had three years before. On that occasion a section of the enlarged vein was removed from the right hip and knee. It had been expertly done, but the postoperative wound did not heal. A large, incurable ulcer appeared. It was this ulcer that brought the railwayman to the clinic.

The doctors saw plainly that the usual treatment would be useless in his case.

They picked a section of skin near the shoulder-blades. It was a rectangle about 5 inches long and 2 inches wide. But the skin was not cut out. It was incised along the two long sides of the rectangle. A thin surgical knife was used to pare it off, and separate it from the underlying tissue. A flap of skin was thus produced, which was connected with the body by its two unincised edges—the short sides of the rectangle.

The surgeon took a needle and silk thread. He folded the two incised edges inward and sewed them together, obtaining a miniature cylinder which was much like the round grip of a suitcase. Sewed up in this way the bleeding inner surface of the flap of skin was protected against infection.

The skin flap did not necrose. Nutrition reached it by the unsevered blood vessels of the two unincised edges of the rectangle.

An incision along one of these edges detached the oblong roll of skin from the body. It no longer resembled a suitcase grip, and took on the appearance of a rounded, pliant stalk, easily bent in any direction. The stalk was ready to start on its journey.

The length of the stalk was measured off along the patient's back in the direction of the affected leg, and an incision made there. The top of the stalk was then bent over, fitted into the incision, and secured in it. In several days it took root.

That was how the flap of skin made its first 5-inch step.

After some time the skin flap was able to make its second step. The second short edge of the rectangle was detached from the body, and made something of a cartwheel to arrive at a new incision prepared for it another length away.

Advancing in this manner along the route mapped out for it by the surgeon, the skin made its journey from the shoulder-blade to the hip, and on to the right knee. Its free end was stitched into the incision made just above the edge of the ulcerated site.

The skin flap had thus reached its destination. That was the final stage of its journey as a "suitcase grip." Now for the final stage of the operation. The farther end of the "grip" was cut off. The stalk-like skin roll stood rooted in the incision on the ulcer border. The sutured side was then incised, and the "stalk" unrolled into a rectangle again. The ulcerating scar on the operation site had been removed and there was a wound in its place. The spread-out "stalk" was placed upon it. The new skin took its designated place, and sutures secured it for good. The transplantation was over.

Today both the initial and improved forms of the operation are known throughout the world as the walking stalk operation. It was evolved by Academician Filatov, the Russian oculist.*

---

*L. Fridland, M.D.: The Achievement of Soviet Medicine, Edited by W. Horsley Gantt, M.D., 1961.

Plastic Operations on the Fallopian Tubes

THOMAS A. STARKEY, M.D.*
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Rochester, Minnesota

THE WRITINGS of Galen suggest that the uterine tubes were known to Herophilus about 300 B.C.; and Ruphus of Ephesus, writing at the end of the first century A.D., noted the presence of these tubes in women, but seems to have regarded them as suspensory structures. Galen in his second-century treatise on gynecology described the uterine tubes in some detail, recognizing for the first time the communication between the tubal lumen and the uterine cavity. It remained for Gabriele Fallopio to provide the first accurate description of the human oviduct in his *Observationes Anatomicae*, published in Venice in 1561:[1]

> That slender and narrow seminal duct rises, . . . from the horns of the uterus itself; becomes, when it has gone a little bit away, appreciably broader, and curls like a branch until it comes near the end, . . . and its end is torn and ragged like the fringe of well-worn garments, and it has a wide orifice which lies always closed through the ends of the fringe falling together; and if these be carefully separated and opened out, they resemble the orifice of a brass trumpet.

The term "fallopian tube" has been universally accepted since the time of Fallopio; it has reached the zenith of eponymic‡ acceptance in medical and anatomic literature, being spelled with a small f.

Surgical procedures on the fallopian tubes include three main types of reconstructive operations: salpingostomy (including salpingolysis), resection with end-to-end anastomosis, and resection with uterotubal implantation. The first case reports appeared during the latter part of the 19th century, when adnexal surgery was being developed. Martin,[2] in 1885, reported the results of the first salpingostomy; in 1894 Mackenrodt[3] noted two successful operations; and in 1900 Goullioud[4] reported a review of the procedure with appropriate drawings. In 1896 Watkins[5] noted a case of successful uterotubal implantation; and Turck[6] in 1909 told of two successes in eight cases of uterotubal implantation.

---

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†Mayo Clinic and Mayo Foundation: Section of Gynecologic Surgery.
‡See Test Your Word Score Page 933.

Plastic tubal operations continued to be done in small numbers through the years, but with such poor results that in 1937 a questionnaire by Greenhill revealed that 56% of the gynecologists condemned the operation.[7] Some improvement in the results of these procedures is evident though, since the advent of the antibiotic era in the late 1930's and since the introduction of polyethylene tubing and Silastic hoods in the early 1950's.

Experimentally, the allantoic membrane was used in humans in the early 1940's in an effort to prevent fimbrial adhesions; tubal patency was obtained in a relatively high percentage, but the conception rate was very poor.[8] Various other ideas have been tried experimentally in lower animals, without much success. These include the use of catgut, bone wax, whalebone filament, and silver wire as stents; the use of resected arteries and veins in place of the fallopian tube;[9] and the use of ileum as a substitute oviduct.[10,11]

O'Neill[12] in 1964 employed the vermiform appendix of a young woman to replace one of her totally fibrosed and occluded oviducts. The organ was patent eight weeks after surgery, but no pregnancy had occurred by the time of his report in 1966.

A device designed to staple the fallopian tube has been reported in the Russian and the English literature.[13] It has been used experimentally in rabbits and dogs, and shows some promise if the technical problems can be overcome.

Anatomy and Histology of the Tube

Anatomically, the fallopian tube is divisible into four parts: the interstitial portion, traversing the muscular wall of the uterine cornua from which the tube arises; a narrow isthmus adjacent to the uterus; the ampulla, which is the widened middle and outer third of the tube; and the fimbria, or infundibulum, representing the outer portion of the tube.

Histologic examination of the fallopian tube reveals three layers: an outer serous layer, a middle muscular layer, and an inner mucous membrane. This inner membrane, known as the endosalpinx, is composed of three types of cells: ciliated, nonciliated secretory, and the intercalary peg cells. The presence of endometrium in the tubal lumen is not uncommon, being found perhaps in as many as 10% of women. The chief significance of this anomaly is in its possible bearing on the etiology of tubal occlusion. The cells of the endosalpinx are influenced by ovarian hormones, and they undergo a histologic cycle corresponding to the various phases of menstruation. The endosalpinx is arranged in longitudinal folds, or rugae, and these rugae divide and subdivide in the more distal portions of the tube, so that a cross section at the fimbriated end reveals a highly aborescent configuration.

Physiology of the Tube

Tubal function was studied by Westman[14] through an "abdominal window" in the rabbit. He found that at ovulation the fimbria are significantly hyperemic, edematous, and distended as they come into direct contact with the ovary. Doyle[15] has taken motion pictures of the ovulatory process via the cul-de-sac; he observed that once the ovum is within the tube, a twofold mechanism propels it toward the uterus: tubal muscle peristalsis and ciliary motion of the endosalpinx. Certain segments of the tube may show antiuterine movement though, and this is believed of importance in establishing union between sperm and ovum somewhere in the distal portion of the tube.

Recently, Pauerstein, Woodruff and Zachary[16] have published a thorough review of tubal physiology, which demonstrates ". . . that the oviduct is not a mere conduit for ova and sperm, but in truth is an organ of exquisite function."

Etiologic Factors

Salpingitis is the etiologic factor in most cases of tubal occlusion, but pelvic adhesions or pelvic scarring, caused by appendicitis or endometriosis, may be the etiologic factor in some cases. The common bacterial causes of salpingitis are gonococcus, streptococcus, staphylococcus, and tubercle bacillus. The gonorrheal type of salpingitis is an ascending infection, causing first an endosalpingitis, then inflaming the other tubal layers as well. If allowed to run its natural course, this type of salpingitis usually leads to partial or complete tubal occlusion. Pyogens, however, make their way outward via the lymphatic channels and blood vessels of the parametrium and broad ligaments. Pyogenic salpingitis is usually associated with postpartum or postabortion infection, rarely with cervical cauterization or uterine curettage. The enlargement of the tube in this type of infection is much greater than with gonococcal salpingitis, but this enlargement is due to interstitial involvement rather than to distension of the lumen. The relative immunity of the tubal mucosa to the pyogens explains the far more favorable prognosis for conception.

Pyosalpinx, hydrosalpinx, and salpingitis isthmica nodosa represent chronic forms of the disease. The first two are sequelae of gonorrhea in most cases, although they may also occur after tuberculosis. Salpingitis isthmica nodosa is also probably of inflammatory origin, although some believe that it results from a process resembling adenomyosis of the uterus; still others have suggested that these lesions represent endometriosis of the tube.

Evaluation

Before reconstructive tubal surgery can be considered, a careful workup of the infertile couple is mandatory. When the husband is known to be fertile, when the results of endocrine and ovulation studies are normal, and when repeated tubal insufflation or hysterosalpingographic studies indicate occluded fallopian tubes, then surgery may be contemplated.

A history of treated gonococcal disease is of importance because most untreated patients and patients with recurrences will have massive adhesions in a rather fixed pelvis, if not tubo-ovarian abscesses. Adequate treatment tends to result in fewer and more filmy adhesions, and hence a better prognosis. A history of appendicitis is also of importance, because this disease, even when it has occurred in the very young, is frequently followed by pelvic adhesions affecting the fimbria. In the Mayo Clinic series,[17] approximately 75% of the patients who underwent reconstructive tubal surgery had previous intra-abdominal or intrapelvic manipulation under a physician's care. Included among these were nine patients who admitted to intra-uterine manipulation in successful efforts at abortion; 14 who had undergone appendectomy presumably for acute appendicitis; and five who had had tubal ligation.

The opportunity for an emergency salpingoplasty may present at any time, when the physician is astute enough to diagnose an early, unruptured ectopic pregnancy. Depending on the condition of the tube at surgery, the conceptus may simply be expressed from the fimbriated end, salpingostomy may be performed, or possibly resection and re-union of the tube.

Operative Principles

Siegler and Hellman[18,19] have stated that it is the burden of the surgeon to devise, at laparotomy and in accordance with the gross abnormality of the tubes, the most logical procedure to produce function. Not surprising then is the large percentage of cases in most recent series that have involved a combination of procedures. Siegler also has made a plea for more uniform recording of the facts in each case,[20] for the sake of better comparison of results in the various series. Mulligan[21] suggested that, if only one adnexus seems reparable, this side should be improved as much as possible and the other adnexus excised in order to secure constant function of the former.

Shirodkar,[22] who perhaps has more experience at tubal plastic surgery than anyone else in the world, has recently outlined some factors affecting prognosis. He said that the results of salpingostomy are better when the uterus is well developed; when adhesions are flimsy and easily separable; when the hydropic fallopian tube returns to near normal size and color, and when the walls of the tube become soft throughout its length. When the fimbria are of normal length and character, the results of salpingostomy may be good; but when the fimbria are distorted or absent, the outlook is poor to dismal. Because a viable tubal ciliary epithelium can be expected with hydrosalpinx of grade 1, the prognosis after tuboplasty is reasonably good.

Operative Procedures

Fimbriolysis and Salpingolysis

The technique consists of gently elevating the fimbrial end of the tube, separating away any thin bands or veils of peritoneum, and at the same time making every effort not to cause bleeding. Adhesions may be separated with fine scissors, by opening the blades of long tissue forceps between the adhesions, by gentle pressure with a gauze sponge, or by division with a cutting cautery. Bleeding may be controlled with hot saline, very fine catgut ties, or cautery, or in some instances by the use of a hydrocortisone rinse.

Salpingostomy

In this procedure the dilated tube is reopened at the fimbria, ampulla, or isthmus. The site is chosen so that the artificial opening in the tube lies in the best possible relationship to the ovary, in order to facilitate entry of an ovum into the tube. There has been little actual change in technique since the turn of the century: an incision is made into the tube, proximal patency is demonstrated, and the mucosa is then everted by numerous interrupted sutures of fine catgut, nylon, or braided silk. The end result may take the form of a cuff, simple stoma, or fishmouth. Again, all bleeding points must be meticulously controlled. Polyethylene tubing may be used as a splint to keep the newly formed stoma open, or a Rock-Mulligan hood made of Silastic may be employed. The polyethylene splint is generally removed in six weeks; the Rock-Mulligan hood requires a second operation, approximately three months later, for removal. Shirodkar[23] recommends tubal irrigation with a solution of penicillin and hydrocortisone at frequent intervals during the first few postoperative days, then every four days until three weeks after the operation. He believes that this method can keep the newly formed stoma open.

Anastomosis

In this procedure the blocked portion of the tube is located and excised, and anastomosis in two layers is accomplished with fine interrupted sutures. Polyethylene tubing is frequently used as a splint, then removed in about six weeks. The point of obstruction may be easily located, according to Siegler,[18] by using a cervical isthmic occlusive clamp and injecting indigo carmine via the fundus. The dye proceeds to the point of obstruction, and when this is relieved, the dye can be readily seen to emerge from the transected end of the tube. The blocked portion also may be located by tubal irrigation, or probing from the distal end. The "pure" anastomosis operation is useful primarily in cases of previous surgical sterilization.

Uterotubal Implantation

The implantation operation has many variations and is often part of a combined procedure. The technique most commonly employed today was reported first in 1932:[24] the tube is divided at the point of obstruction, the occluded cornual portion reamed out, and the patent residual tube pulled into the uterus and held there by sutures.

As Pratt and associates[25] describe their technique, the tube is first irrigated with saline to determine whether any obstruction exists distal to the cornua. After the tube is divided and the lumen is rechecked, the medial end is split and fine catgut sutures are stick-tied to each side. An opening is then made through the uterine cornua into the endometrial cavity either by reaming with a 5-mm punch, or by coring with a narrow-bladed scalpel. The blunt end of a large, curved needle is then passed into the uterus posteriorly and out the newly formed opening. The needle is threaded, and the suture is pulled through the posterior uterine wall. This process is repeated anteriorly; then by means of gentle traction, the fallopian tube is pulled through the uterine horn into the endometrial cavity. The newly implanted fallopian tube is then fixed externally by several sutures from the tubal serosa to the uterine wall.

Results

The results of plastic operations on the fallopian tube are generally discouraging—in terms of patency, conception, and live births. In 1960, Puigmacia[26] compiled and reviewed the results obtained by 66 surgeons who had done approximately 3,000 operations (Table 1). The incidence of ectopic gestation in this review was 2.68% with a slightly lower incidence in the cases in which polyethylene was

TABLE 1

Pregnancy After Tubal Plastic Surgery*

Procedure	Cases	Per cent of normal pregnancy
Salpingolysis	264	35 11
Salpingostomy	1,936	14.71
With polyethylene	559	17.53
Without polyethylene	1,377	13.58
Tubal implantation	203	27.96
Anastomosis	92	11.96

*Modified from Puigmacia, L. P.: Cited by White, Margaret M., and Green-Armytage, V. B.: The Management of Impaired Fertility. London, Oxford University Press, 1962, p. 241.

not used.

A number of series have been reported since 1960. Because of a lack of uniformity in evaluation, technique, and follow-up, it is not possible to make useful comparisons. Siegler and Hellman[19] in 1963 reported a critical analysis of their 43 cases (Table 2). Mulligan[21] reported his results from salpingostomy in 1966; he employed the Rock-Mulligan hood in all cases (Table 3). He advised that the prosthesis be removed by laparotomy, not via the cul-de-sac, at least 12 weeks after the operation.

Mroueh and associates[27] reported the Yale Medical Center experience with 40 infertile patients undergoing surgical treatment of tubal occlusion or pelvic adhesions (Table 4). They pointed out that only two term pregnancies occurred among the 32 patients who required bilateral surgery. The best results were obtained with patients needing only lysis of adhesions; among those with implantation operations, no pregnancies occurred. It is their belief that significant improvement in the results of tubal surgery will not come from further refinement in technique, but must come from increased knowledge of tubal function and physiology so that a more rational selection of cases for surgery can be made.

Hanton, Pratt, and Banner[17] reviewed the Mayo Clinic experience with tubal plastic surgery from 1945 through 1962, a total of 75 patients (Table 5). Fifty-four of these patients were studied in the immediate postoperative period for tubal patency; 74% had patent tubes. But when these patients were restudied from one month to 10 years later, the percentage dropped to 55%. Antibiotics were used preoperatively in some but with no great increase in the success rate. Polyethylene splints were used in only five patients, but no pregnancies occurred; Rock-Mulligan hoods were not used in any patients in this series. The presence of obvious hydrosalpinx or pyosalpinx in those patients who had salpingostomy appeared to be a poor prognostic factor.

Conclusion

The objective of plastic operation on the fallopian tube must be to achieve some semblance of normal function, not merely to achieve patency. Israel[28] reminds us that the fallopian

TABLE 2

Pregnancy in 43 Cases After Tubal Plastic Surgery*

			Pregnancy		
Procedure	Cases	Patency	Abortion	Ectopic	Viable
Salpingostomy	6	0	0	0	0
End-to-end anastomosis	3	5	0	0	1
Uterotubal implantation	6	0	0	0	0
Combination procedure	28	0	0	0	2

*Modified from Siegler, A. M., and Hellman, L. M.: The Tubal Plastic Operation: A Critical Analysis of 43 Cases. Fertil Steril 14:300 (May-June) 1963.

TABLE 3

Results in 45 Cases of Salpingostomy*

	Pregnancy			
Patency	Abortion	Ectopic	Term	Live births
39	3	4	9	14

*Modified from Mulligan, W. J.: Results of Salpingostomy. Intern J Fertil 11:424, 1966.

TABLE 4

Pregnancy in 40 Cases After Tubal Plastic Surgery*

			Pregnancy		
Procedure	Cases	Patency	Abortion	Ectopic	Term
Salpingolysis	14	11	0	1	5
Fimbrioplasty	15	12	0	1	2
Reimplantation	9	4	0	0	0
Combination procedure	2	1	1	0	0

*Modified from Mroueh, A., Glass, R. H., and Buxton, C. L.: Tubal Plastic Surgery. Fertil Steril 18:80 (Jan.-Feb.) 1967.

TABLE 5

Result of Primary Pregnancies in 75 Cases After Tubal Plastic Surgery*

		Pregnancy		
Procedure	Cases	Abortion	Ectopic	Live births
Salpingostomy	32	4	1	1
End-to-end anastomosis	2	1	0	0
Uterotubal implantation	22	0	0	10
Combination procedure	19	0	0	1

*Modified from Hanton, E. M., Pratt, J. H., and Banner, E. A.: Tubal Plastic Surgery at the Mayo Clinic. Amer J Obstet Gynec 89:934, 1964.

tube is more than just a passageway; the freedom of its fimbria, the peristalsis of its muscles, the motion of its cilia, and the secretions of its cells are all necessary to its reproductive physiology.

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It's the Law

NO LIABILITY FOR ELECTROSHOCK THERAPY INJURIES

A 74-year-old patient was diagnosed as suffering from manic depressive psychosis and was hospitalized for electric shock treatments.

During the second treatment, a cracking sound was heard. It was later determined that she had suffered bilateral fractures of the acetabula.

Since fractures are a recognized risk with electric shock therapy, the mere presence of the fractures was not evidence of negligence.

Pendleton v. Burkhalter, 432 S.W. 2d 724 (Tex., May 16, 1968: on rehearing, September 5, 1968: rehearing denied, October 24, 1968). The Citation, Vol. 18, No. 8, February 1, 1969.

Tough Treatment

An old lady fell down the stairs and broke her leg. The doctor put it in a cast and warned her not to walk up and down the stairs. The leg was slow in mending. Finally, after six months, the doctor announced it was all right to remove the cast.

"Can I climb the stairs now?" asked the old lady.

"Yes," answered the medical man.

"Oh, I'm so glad," she chortled. "I'm sick of climbing up and down the drainpipe all the time."*

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*Maxwell Droke: The Speaker's Handbook of Humor.

No man would listen to you talk if he didn't know it was his turn next.—Ed Howe

Corrosive Esophagitis*

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DESPITE PUBLIC EDUCATION efforts and the labeling of poisons, there remains a large number of patients seen annually with severe caustic burns. The great majority of these patients are children under the age of five years who have accidentally ingested a potent caustic. Often the severely burned are at least mildly mentally deficient or have neglectful parents. Adults ingesting corrosive agents usually do so in a suicide attempt. Rarely is homicidal intent implicated.

Treatment includes immediate life-saving care and often long-term management of a permanently altered hypopharynx and esophagus. The most common areas of severe burn are the esophageal introitus, the aortic knob area, and the esophagogastric junction.

In severe corrosive burns, the larynx and stomach may also be involved[3].

Caustic Agents

Lye is the most devastating caustic agent ingested by man. Unfortunately, when in solution, it has a white color, and children may mistake it for milk. Drano and Sani-flush, commercial agents found in nearly every home, are also capable of producing severe burns. Less frequently ingested, and somewhat less potent, are phenol, lysol, potassium permanganate, and the strong acids. Acids have a tendency to coagulate the superficial layers of the esophagus, forming a firm eschar which limits deeper burning. The acids, however, may cause serious gastric burns[8]. Clorox ingestion has been found to cause little damage to the oral mucosa and esophagus, prompting several investigators to challenge the need for esophagoscopy and treatment of these patients[5].

Diagnosis

The history is usually vague concerning the amount of material ingested, making judgment

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on history alone unreliable. It is helpful if the agent ingested is brought with the patient. Careful physical examination of the mouth for evidence of burns is mandatory. While a severe esophageal burn may co-exist with an unburned mouth, this is an unusual circumstance occurring when a dilute solution does not penetrate the oral salivary coating. Contrariwise, oral burns often, but not always, are associated with esophageal burns. Waggoner[8] found that eight of 43 patients with mouth burns had esophageal burns requiring treatment; Cody[1] found that 12 of 23 mouth burns showed associated esophageal injury.

The diagnosis of esophageal burns ultimately depends on endoscopic findings. While endoscopy should be done as soon as the patient's general status permits, it is wise to wait approximately 24 hours post injury to allow development of recognizable eschar and ulceration. Immediate esophagoscopy may reveal only erythema and edema. The esophagoscope is advanced only far enough to establish the diagnosis of a severe or circumferential burn and is then withdrawn. Further advancement is hazardous. The hypopharynx and larynx are closely inspected for evidence of burns.

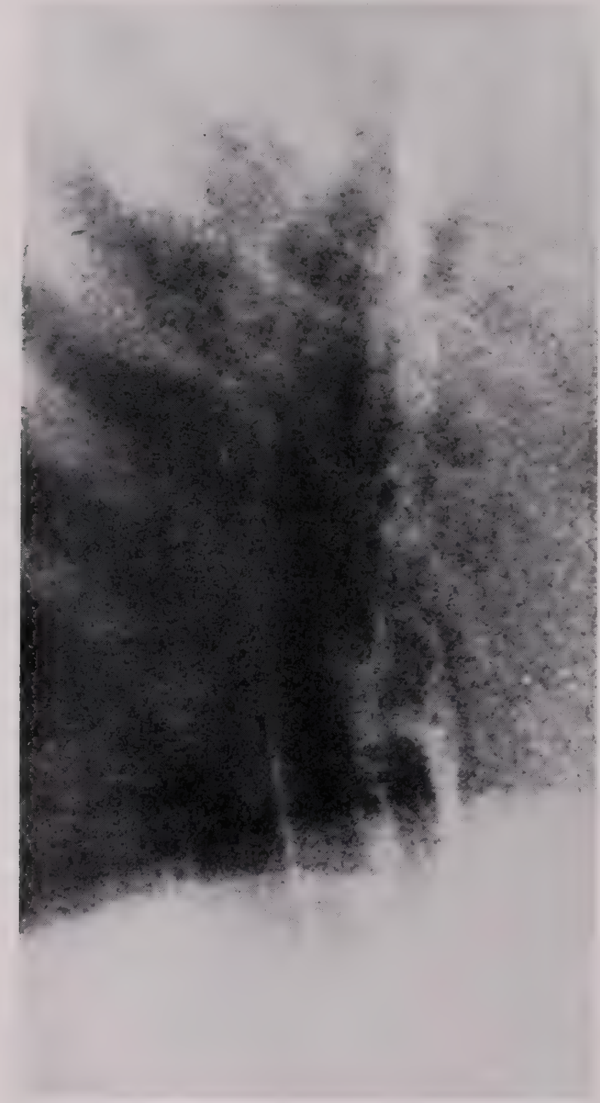

Fig. 1—Case 1. Aperistaltic dilated esophagus eleven days post lye ingestion. Patient receiving steroids.

Pathology

An excellent experimental study on dogs by Johnson[4] has defined three phases in the course of corrosive esophagitis.

The Acute Phase

The acute necrotic phase occurs one to four days post injury. There is death of cells secondary to coagulation of intracellular protein. Vessel thrombosis and bacterial infiltration is seen.

Ulcerative-Granulation Period

The ulcerative-granulation tissue phase follows the slough of superficial necrotic coagulated tissue at three to five days. This leaves an acutely inflamed ulcerated lesion which by the end of the first week is covered with fresh superficial granulation tissue containing blood vessels and fibroblasts. Collagenous connective tissue is seen at 10 to 12 days.

Stricture

Cicatrization and stricture formation may be noted by three to four weeks when collagenous material begins to contract. The superficial inflammatory tissue progresses slowly until four to eight weeks when reepithelialization occurs. It is during the second month that clinical vigilance is necessary to pick up early stricture formation.

Treatment

As early as 1950 cortisone was reported to exhibit an anti-inflammatory effect and inhibit fibroplasia in wounds.[6] This stimulated interest concerning its use in esophageal burns. Since bacterial invasion is also seen following burn injury, it was postulated that antibiotics might also be useful. Johnson's experimental study on dogs with burned esophagi included the use of antibiotics and steroids alone and in combination. He found that the use of antibiotics alone promoted early granulation tissue formation and hastened its maturation. This resulted in *earlier* stricture formation.

Steroids alone prevented much of the early inflammatory reaction, repressed the granulation tissue response, and inhibited fibroplasia. The incidence of narrowing and stricture formation was much less than in the control animals and those treated with antibiotics alone.

The animals treated with both antibiotics and steroids showed the lowest incidence of stricture and the least inflammatory reaction.

Delayed institution of steroid therapy beyond two to six days post ingestion was not as efficient in preventing the intense inflammatory response and later stricture.

From these studies we may extrapolate useful guidelines for the treatment of patients ingesting corrosive substances. For convenience, treatment will be divided into immediate, intermediate, and long-term.

Immediate Treatment:

Severely burned patients are often in shock and require supportive measures. Intravenous fluids, including blood or other volume expanders, may be necessary. Intraoral, hypopharyngeal, and laryngeal edema may compromise the airway, necessitating tracheostomy. Vomiting is not induced, as it is always too late and may cause further injury. Likewise, the use of mild acids to neutralize the strong base is too late.

Esophagoscopy should be done between 12 and 24 hours post ingestion to establish the diagnosis of esophageal burn. This timing seems appropriate because it is delayed long enough to permit the development of recognizable pathology and yet provides an early diagnosis which dictates the therapeutic regimen. Diagnostic esophagoscopy at seven to 10 days may constitute an unwarranted delay if the burn was not suspected and no treatment had been given. In addition, the burned esophagus is weakest at that time, making the procedure more hazardous.

Once the diagnosis of esophageal burn is established, the patient should swallow a heavy # 4 or D button-hole twist braided silk string. The proximal end is brought out through the nose and either taped to the head or looped around the ear. This string serves as an important guide for later antegrade or retrograde dilatations. If the burn is severe, a gastrostomy should be done, permitting retrograde dilatations and feedings. In this case the distal end of the swallowed string is brought out the gastrostomy opening and tied to the proximal end of the string, creating a continuous loop. Irritating nasogastric tubes may contribute to the inflammatory response and are best avoided.

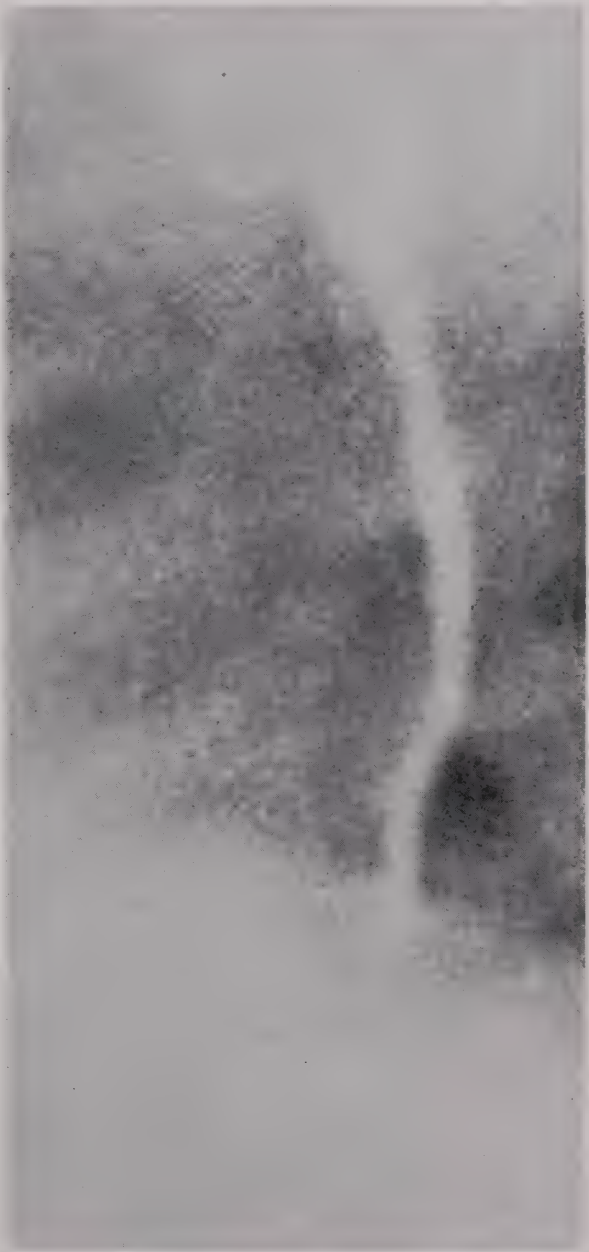

Fig. 2—Case 1. Diffusely narrowed esophagus twenty-one days post lye ingestion and three days following cessation of steroids.

Antibiotics and steroids are begun when the diagnosis is established, provided there are no definite contraindications such as tuberculosis or peptic ulcer disease. The dosage of prednisone in a 70 kg man is 20 mgm qid, tapered down to 5 mgm qid over seven to 10 days. Children are given one half the adult dose. Antacids are given routinely. Oral burns can be comforted by use of bismuth subcarbonate powder. Children will tolerate this if it is sprinkled on marshmallows.

Intermediate Treatment:

Antibiotics may be discontinued after two weeks since their major role is to decrease the inflammatory response secondary to early bacterial invasion. Steroids are continued at a maintenance level for eight weeks, since the epithelialization may not occur until that time.

Esophageal Bouginage or Dilatation

The role of bouginage* and when it should be started have never been clearly resolved. Advocates of early bouginage[2] feel that the prevention of stricture formation outweighs the risk of perforation during this time when the burned esophageal wall is at its weakest. Others[7] feel that early dilatation is too hazardous and that later bouginage is adequate.

Blunt Dilator

The simplest method is peroral passage of a blunt rubber mercury-filled Hurst dilator. While following the path of least resistance has great application in well-established esophageal strictures, this feature is undesirable and dangerous in an acutely burned esophagus with weak walls, pocketing, and irregularities. For this reason the Hurst dilator is rarely used in the acute situation and is reserved for management of the chronic strictures.

Dilator Over String

Peroral passage of a dilator (e.g., Sippy, Peustow, Plummer) over a previously swallowed string, while safer than the blind passage of dilators, does not entirely eliminate the possibility of the dilator tip being imbedded in a pocket in the esophageal wall. This type of dilatation avoids the need for a gastrostomy; however, it should never be used if the patient has a gastrojejunostomy, as the string may loop around and strangulate the gut.

Retrograde Dilatation

The safest method is retrograde dilatation via gastrostomy. Gastrostomy should be done early so that healing occurs by the time dilatation is started. Dilatation is accomplished by passing consecutively larger, tapered Tucker dilators through the gastrostomy, up the esophagus, and out through the mouth. The dilators are tied together end to end with an intervening length of heavy, black silk at least as long as the distance from the gastrostomy to the mouth. Since tension can be kept on the string at both the gastrostomy site and the mouth as the dilators are being passed, there is no danger of perforation by false passage. Its greatest application is in the early and intermediate treatment of burns.

While not trying to avoid this issue, we feel that each case must be individualized, and if early dilatation is felt to be necessary, it should be done in the safest manner possible, namely, retrograde dilatation via a gastrostomy using Tucker dilators. For lesser burns, antegrade dilatation begun at a later, safer date is felt to be adequate.

Periodic esophograms beginning two to three weeks post ingestion are of value in determining the extent of scarring and whether any circumferential scarring has occurred.

Long-term Treatment:

Many patients will require periodic bouginage for several years or for life. A schedule is determined which achieves and maintains an adequate esophageal lumen between dilatations. This can vary from a day to months. Antegrade Hurst dilators are most frequently used and many patients can manage this at home.

There are some patients who cannot be successfully dilated by this method because of complete stenosis, scarring with marked pocketing and irregularities; or because they refuse dilatations.

Surgical excision of the strictured area or bypass via an esophagocologastrostomy or pharnygocologastrostomy is the current surgical treatment of choice.

Sudden difficulty with dilatations or increased dysphagia should alert the physician to a possible neoplasm in the esophagus.

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*See Test Your Word Score Page 933.

Case Reports

These cases were selected to illustrate the great disability that a severe burn can cause and the immediate and long-term treatment necessary in their care.

Case 1:

This two-and-one-half-year-old retarded boy ingested "Lewis Lye" on August 9, 1965. He was treated in an emergency room in South Dakota with oral milk and "gastric lavage." Later the same day he was transferred to University of Minnesota Hospital. On examination he was found to be acutely ill with first degree burns on his anterior thorax and abdomen. Supportive measures, including intravenous fluids, were instituted, and Solu Cortef 40 mg intravenously q6h was begun. Aqueous penicillin 600,000 u q6h and chloromycetin 250 mg q6h were started. Because of respiratory distress from laryngeal edema, a tracheotomy was performed in the operating room that same day. Examination there revealed burns of the tongue, lips, bucco-alveolar gutters, soft and hard palate, epiglottis, and right aryepiglottic fold. The vocal cords appeared normal. There was evident coagulation necrosis of the esophageal introitus, and the esophagoscope was not passed further. A gastrostomy was performed on August 11 for purposes of feeding and dilatation. Several days later the patient swallowed a string which was then pulled out through the gastrostomy opening. A cine esophagram, August 20, (Figure 1) showed a dilated esophagus exhibiting poor peristalsis. The penicillin and chloromycetin were discontinued August 20, and the patient was tapered off steroids by August 27, because of a mumps epidemic on the ward. A repeat study on August 30 (Figure 2) revealed severe diffuse narrowing below the aortic knob. Retrograde dilatation was begun August 31, as soon as the results of the latter cine esophagram were known. Biweekly or weekly retrograde Tucker dilatation was done until early October 1965 when antegrade Hurst dilatation was started. The tracheotomy was also discontinued at that time.

Since November 1, 1965, the mother has dilated the patient at home with a #24 F Hurst dilator. Except for two episodes of obstruction requiring retrograde dilatation in the hospital, she has managed this successfully. In January of 1967, the gastrostomy was removed.

This case represents the average *severe* burn, i.e., one requiring emergent supportive and long-term care. The points of special interest are the initial cine esophagram which showed dilatation 11 days post ingestion and the esophagram 21 days post ingestion that revealed a marked narrowing of the esophagus. It should be noted that steroids had to be discontinued 18 days post ingestion. Our present regimen includes steroids for up to two months or until such a time as esophagoscopy shows re-epithelialization of the esophagus.

One should not be encouraged by an esophagram showing dilation, since this merely precedes later stricture if there are raw surfaces or areas of incipient fibrosis and scarring.

Case 2:

This two-year-old boy was first seen at Ancker Hospital in November 1964 for Drano ingestion. The initial laryngoscopy revealed extensive burns of the entire oropharynx and hypopharynx. The larynx was also felt to be involved. Treatment consisted of tracheotomy, gastrostomy, steroids, penicillin, chloromycetin, and early retrograde dilatation. He was transferred to University of Minnesota Hospitals in April 1965 because of repeated aspiration pneumonia. Examination revealed a severely scarred hypopharynx which was funnel-shaped and directed into the glottis. Because all secretions and oral fluids were directed straight into the glottis, a laryngectomy had to be performed. Since that time the patient has required retrograde dilatations which are presently done biweekly. He is able to swallow his oral secretions and small amounts of liquids. His major nutrition must still be supplied via gastrostomy feedings. The possibility of learning esophageal speech is remote because of the severe oral and esophageal scarring.

This case represents perhaps the ultimate tragedy short of death attendant on ingestion of a caustic. The hypopharyngeal and oral scarring prevent successful esophagectomy and bypass procedures. The laryngectomy, while life-saving, rendered him speechless.

Summary

The accidental ingestion of corrosive substances continues to be an all too common tragedy in the pediatric age group. Diagnosis is dependent on careful physical examination and esophagoscopy. Based on experimental studies and clinical series, the early use of antibiotics and steroids reduces the inflammatory response and appears to prevent or minimize later stricture formation.

Dilatation is often necessary in the treatment of chronic strictures, and its early use may play a role in the prevention of permanent stricture. Occasionally, surgical removal of isolated areas of stricture formation or bypassing a severely burned esophagus is indicated. Intelligent, individualized early management and long-term care are requisite in the complete care of these patients. Public interest in the problem should be aroused, as preventive medicine is crucial.

References may be secured from the authors.

Famous Men and Their Bad Health

"Here I Stand"

Martin Luther

"The just shall live by faith!"

This was Martin Luther's unqualified declaration after a flash of sublime insight released him from his commitment to corrupt Catholic doctrine.

Only through the prism of his Olympian soul struggle and cataclysmic spiritual revolt can we assess the man health-wise. Never rugged physically, weakened by stern monastic asceticism, plagued by numerous chronic ailments, prematurely old and overweight, haunted by imaginary guilt and remorse, pursued by delusions—all under the shadow of heresy: these formed the constellation of Luther's infirmities.

Though Luther was probably not neurotic, his early physical symptoms were of a "nervous" character: dizziness, head noises, stubborn constipation, urine retention, insomnia. In fact, he ruefully called himself a Lazarus. Of his constipation he once wrote to a friend: "The trouble with which I suffered at Worms has not left me but increased, for I am more constipated than ever in my life and despair of a remedy. The Lord thus visits me that I may not be without a relic of the cross. Blessed be He. Amen." From this we can deduce that Luther regarded illness as divinely ordained—if not actually imposed.

In addition, there was profound dejection at his failure to measure up to the lofty stature he thought God expected of him. Here he was sure that the Devil was sabotaging his efforts. Sometimes when Luther was concentrating on his studies, Satan, with deliberate malice, made so much noise by pounding on the walls or rattling nuts in a can that Luther was obliged to abandon his books and retire.

While Luther believed sickness was God-ordained, he was too practical to spurn materialistic medication. On one occasion during his youth when he was confined to bed with a raging fever and was denied liquids—as was customary then—he crawled unseen to a pail of water and drank himself full, a measure which induced abundant sweating and probably saved his life. During another severe illness he repudiated an invalid's vapid diet, called instead for fried herring and cold peas, consumed them, and was none the worse for his indiscretion—if indiscretion it was. On a later occasion, during an agonizing kidney-stone attack away from home, his wife wrote to him recommending a mixture of garlic and horse dung. Unabashed by the revolting concoction, Luther swallowed it, then tersely wrote his wife: "Your medicine did not help me."

One of Luther's biographers, Ewald Plass, gives this stark and succinct resume of Luther's ailments: "Luther, from his fortieth year onwards, was a sick man. After he had suffered for six months, in 1521, from severe digestive troubles, he was attacked in 1523 by a nervous affection of the head, which soon became permanent. In 1526 he developed a severe stone in the kidneys, with all possible accompaniments—feverish rheumatism, sciatic conditions, boils, etc. In addition to this he suffered very frequently from obstinate catarrh and digestive trouble, also, transitorily, from hemorrhoids (1525), dysentery (1528), a running inflammation of the ears (1527), which for weeks deprived him of sleep and hearing, toothache, and fearful nervous constriction of the chest (1527)."

Luther died of a heart attack in 1546, at the age of 63.

To read Luther's life is both exhausting and exalting: exhausting as we endure vicariously with him his manifold physical morbidities and spiritual torments, and exalting as we identify with him in his victorious transcendence of both.

Only in such Titanesque world figures as Martin Luther does the immortal spark so illumine the mortal clay as to triumph over it so gloriously!

With acknowledgments to Ewald Plass: This Is Luther, 1948.

Tumors of the Upper Lip

Benign and Malignant

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LEWIS B. WOOLNER, M.D.‡
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Because of their infrequent occurrence, tumors of the upper lip seldom have been studied separately; instead, they have merely been included in reports on tumors of the lower lip, oral cavity, salivary glands, and skin. However, since some growths on the upper lip present distinctive features, detailed consideration of them seems worthwhile. Consequently, we reviewed the clinical and pathologic characteristics, the treatment, and the prognosis of tumors involving the upper lip, which have been seen on our service at the Mayo Clinic.

Materials and Methods

The records of all patients with benign and malignant lesions of the upper lip who were examined at this clinic from 1944 to 1963 inclusive were abstracted. After exclusion of cases in which tumors originated in adjacent tissues and invaded the upper lip by direct extension, 702 cases remained. Except for 133 angiomas treated without microscopic confirmation, diagnoses were definitely established by reexamination of the original microscopic sections. When slides were not available, paraffin blocks of preserved tissue were prepared and additional sections were made. Follow-up information on each patient was acquired through return visits to this clinic or by direct correspondence.

Results

The 702 tumors, 272 (38.7%) benign and 430 (61.3%) malignant, were fairly evenly distributed between the sexes (Table 1). Of patients having benign lesions, 145 (53.5%) were female and 127 (46.7%) male; of those having malignant lesions, 235 (54.7%) were male and 195 (45.4%) female.

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†Section of Plastic Surgery, Mayo Clinic and Mayo Foundation, Rochester.

‡Section of Surgical Pathology, Mayo Clinic and Mayo Foundation, Rochester.

Benign Lesions

Angioma

Of 194 angiomas, cavernous and capillary, 52.6% were apparent at birth and 80.3% were noted during the first year of life. A majority of the affected patients (58.8%) were female. Although the dimensions were recorded in only 96 cases, most of these lesions (72.9%) were comparatively small, 0.1 cm to 1 cm in diameter. In 128 cases (66.0%) treatment consisted of irradiation (usually interstitial radiation involving implantation of radon seeds) or complete or partial excision with or without a skin graft. Radiation therapy was used in 60 (46.9%) of these 128 cases.

Mixed Tumor

Only two of the 24 mixed tumors were adherent to the skin; the others were located in the substance of the upper lip, unattached to skin or mucosa. Two thirds of the tumors became apparent when the patients were 30 to 59 years of age. Although mixed tumors can be painful, usually patients complained only of a lump in the lip. Treatment consisted of wide excision with primary closure of the wound or with local plastic repair. Four patients were lost to follow-up, but the others remained free of any evidence of recurrence at the time of follow-up study or of death, a matter of seven to 17 years after initial treatment.

Keratoacanthoma

The six patients having keratoacanthoma* ranged in age from 46 to 80 years, and the lesions varied from 0.3 to 1.5 cm in diameter. The average duration of these tumors was relatively short, about nine weeks, which is one clinical feature that distinguishes keratoacanthoma from basal-cell carcinoma. Four patients were treated by excision and primary closure

TABLE I

Classification of Tumor and Age and Sex Distribution of Patients

Type of lesion	Number	Per Cent	Male	Female	Average age, yr
Benign	272	38.7	127	145	53*
Neoplasms	231	85.0			
Angioma	194	71.3	80	114	
Mixed tumor	24	8.8	14	10	52
Keratoacanthoma	6	4.9	3	3	66
Neurogenic tumor	4		1	3	44
Leiomyoma	1		0	1	69
Papilloma	1		0	1	9
Calcifying epithelioma	1		1	0	55
Hyperplastic lesions	24	8.82			
Hyperkeratosis	13		11	2	58
Epithelial hyperplasia	6		4	2	53
Sebaceous gland hyperplasia	3		1	2	66
Leukoplakia	2		1	1	58
Inflammatory lesions	12	4.42			
Granuloma	5		4	1	47
Nonspecific inflammation	5		3	2	59
Abscess	2		1	1	67
Cysts	5	1.84			
Mucous cyst	3		2	1	59
Epidermoid cyst	2		1	1	46
Malignant	430	61.3	235	195	60
Basal-cell carcinoma	315	73.3	156	159	60
Squamous-cell carcinoma	100	23.3	71	29	59
Cylindroma	4	3.5	1	3	48
Lymphoma or leukemic infiltrate	4		4	0	56
Malignant melanoma	3		1	2	52
Metastatic carcinoma	3		3	0	65
Adenocarcinoma	1		0	1	81
Total	702				

*Ages of patients having angioma were ignored in determining this average.

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*See Test Your Word Score Page 933.

and one patient by excision and electrocoagulation of the base. Although one patient could not be traced, there were no recurrences in the other five cases after follow-up of five months to 11 years.

Miscellaneous Benign Tumors

These included three neurofibromas, one neurilemmoma,* one leiomyoma, one papilloma, and one calcifying epithelioma of Malherbe. Simple excision proved to be adequate therapy.

Hyperplastic Lesions

These lesions included only two instances of leukoplakia, in marked contrast to the frequency with which leukoplakia of the lower lip is encountered. All 24 lesions were excised and none recurred. The average age for the 17 male and seven female patients was 58 years.

Inflammatory Lesions

The 12 patients with inflammatory lesions averaged 55 years of age. Treatment consisted of antibiotic administration, excision, or incision and drainage, as indicated.

Cysts

The three mucous and two epidermoid cysts presented no diagnostic or therapeutic problems.

Malignant Lesions

Basal-Cell Carcinoma

Basal-cell epitheliomas comprised 73.3% of the malignant tumors and 82.6% of the carcinomas involving only the skin surface. There was an even sex distribution. The exact location was specified in 241 of the 315 lesions; 200 were located on the skin surface and 41 at the mucocutaneous junction where they were considered to have arisen from the skin. Tumor size was indicated in only 255 cases; it ranged from 0.1 cm to 5 cm.

The presenting signs and symptoms were those common to basal-cell carcinoma in any location, such as a cystic-appearing growth with or without ulceration, with scaling or crusting, and with evidence of rolled pearly borders.

Although excision with electrocoagulation of the base was employed in some cases, the most common method of treatment was excision—with primary closure of the wound in most instances, but with the use of a skin graft in a few. Irradiation was used in only four cases. There were 18 recurrences of which 16 could be controlled surgically; in the two remaining cases, the patients were lost to follow-up. The five-year survival rate was 86.0% (Table 2).

TABLE 2

Five-Year Survival Rates of Patients With Carcinoma of the Upper Lip

	Patients		Lived 5 or more years after treatment*	
Carcinoma	Total†	Traced	Number	Per cent
Squamous-cell				
Cutaneous	50	45	38	88.4
Mucocutaneous	9	9	7	77.8
Vermilion	17	15	11	73.3
Mucosal	6	6	2	33.3
Basal-cell	232	207	178	86.0
Total	314	282	236	83.7

*Based on traced patients; inquiry as of January 1, 1964.
†Includes only those patients treated in 1958 or earlier.

Squamous-Cell Carcinoma

Sixty of the 100 squamous-cell carcinomas of the upper lip were located on the skin surface, 11 on the mucocutaneous border, 18 on the vermilion portion of the lip, and seven on the mucosal surface. The locations of four lesions were not given. Of patients with this disease, 71.0% were male.

The most common presenting symptoms in cases of squamous-cell carcinoma of the upper lip were scaling, crusting, and ulceration; the most common signs were ulceration, crusting, keratotic change, thickening, and induration.

The problem of metastasis to cervical lymph nodes is much less serious in carcinoma of the upper lip than in that of the lower. Cervical lymph nodes were palpable on admission in seven of the 100 cases of squamous-cell carcinoma of the upper lip. Metastasis to regional lymph nodes occurred in only six cases. Although only the submaxillary group of lymph nodes was involved in five of these cases, distant metastasis did develop in the sixth case.

Except for three cases in which irradiation was employed, the squamous-cell epitheliomas in our series were treated by excision and primary closure or, in a few instances, by excision and electrocoagulation.

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*See Test Your Word Score Page 933.

Local recurrence was a problem in 13.3% of carcinomas involving skin surface, in none of those of the mucocutaneous border, in 11.1% of those on the vermilion portion, and in 42.9% of those originating on the mucosal surface.

The five-year survival rate was 77.4% (Table 2).

Cylindroma

Patients with cylindroma of the upper lip ranged in age from 35 to 60 years, and the duration of the disease before they sought treatment at this clinic averaged 5.7 years. While these patients complained mainly of a lump or of thickening of the lip with some soreness, the only physical sign of any importance was an indurated nodule or mass within the substance of the lip.

Two of the four patients were treated by excision and electrocoagulation, one by electrocoagulation alone, and the fourth, who had a recurring cylindroma, by interstitial irradiation in the form of radon seeds. Two patients had metastasis, and one of these also showed evidence of local recurrence; however, despite local recurrence and regional and distant metastasis, the latter individual was living seven years after the initial treatment. The other patient had pulmonary metastasis and was lost to follow-up study. The two patients without metastasis were living 16 and 18 years after treatment of the primary lesion; they showed no signs of local recurrence or metastasis.

Malignant Melanoma

All three patients with malignant melanoma—two female, 63 and 34 years old, and one male, 60 years old—had treatment prior to their registration at this clinic. Treatment here consisted of excision and electrocoagulation in one case and excision of scar tissue (no evidence of residual tumor) in the second. No local recurrence or metastasis was ever found in these cases after seven and five years, respectively. The third patient received no treatment and was subsequently lost to follow-up.

Other Malignant Tumors

The remaining eight tumors included one adenocarcinoma (arising on the midcutaneous surface of the upper lip of an 81-year-old woman), three lymphomas, one leukemic infiltrate (in a four-year-old boy), and three metastatic carcinomas. In regard to the last three tumors, the primary lesions were located in the kidney, rectosigmoid colon, and lung, respectively.

Comment

Benign Lesions

Although angiomas of the upper lip can make their appearance at any age, 80.3% of such lesions in our study were noted during the first year of life. These findings correspond with those reported by other authors concerning hemangiomas in general.[1,2] Since there is no uniformity in the care of patients with angiomas at various medical centers, the treatment of these lesions presents a complex problem. However, since many angiomas undergo spontaneous regression, it probably is preferable in most cases *to defer any treatment for the first two years of life* or until one is certain that there is little likelihood that the lesion will disappear. Small angiomas should usually be removed surgically, especially if they can be excised without distorting the lip. Large ones which do not regress are often best treated initially by means of interstitial irradiation in the form of radon seeds; this practically always produces some shrinkage. Subsequently, plastic surgical techniques can be employed to improve the appearance and contour of the lip.

Aside from angiomas, mixed tumors are the most common benign tumors to involve the upper lip. Excluding the angiomas, 24 (64.8%) of the 37 benign tumors in our series were mixed tumors. Chaudhry and co-workers[3] found that 61% of all intra-oral minor salivary gland tumors were benign, that 39% were malignant, and that mixed tumors comprised 56% of all the benign and malignant neoplasms. Except for the palate, they found the upper lip to be the most common location. Among the nodules located in the substance of the upper lip, mixed tumors are more frequently encountered than any other type of benign growth. The likelihood of a nodule in the substance of the upper lip being either a mixed tumor or a cylindroma is 72.4%; consequently, such nodules should not be disregarded. Because a mixed tumor is usually well encapsulated, it can be satisfactorily treated by simple excision. Should the overlying skin or mucosa be adherent, the attached epithelium should be removed along with the tumor.[3]

The diagnosis of keratoacanthoma is based on the history, the appearance of the lesion, and the microscopic picture. Often confused with basal-cell carcinoma, keratoacanthoma cannot be diagnosed with complete certainty until a specimen is examined microscopically. Treatment of this type of benign lesion involves nothing more than simple excision.

Malignant Lesions

About 2.1% of cutaneous epitheliomas occur on the upper lip; of these, nearly 80% are basal-cell carcinomas; the rest are squamous-cell carcinomas.[4,5] In the present study, 381 malignant lesions involved the cutaneous surface of the upper lip, of which 315 (82.7%) were basal-cell carcinomas and 60 (15.8%) squamous-cell. Male and female patients were equally affected by basal-cell carcinomas of the upper lip, while 73.3% of the squamous-cell carcinomas of the skin occurred in men. The average ages of patients having basal and squamous-cell carcinomas in our series (Table 1) were similar to those reported by other authors.[4,5]

Squamous-cell carcinoma of the vermilion portion of the upper lip is relatively rare. During 20 years only 18 cases of squamous-cell carcinoma of this part of the upper lip were found, as compared to 1,802 cases of the lower lip—a ratio of 100 to one. Of the squamous epitheliomas on the vermilion part of the upper lip, 77.8% affected patients from 50 to 79 years of age, which is similar to the age-related incidence for such involvement for carcinoma of the lower lip. Only 1% to 3% of such carcinomas of the lower lip affect female patients.[6-8]

Metastasis of squamous-cell carcinoma involving the skin of the upper lip in this study occurred in five of 60 cases (8.34%)—noted on admission in one case and during follow-up examinations an average of one year after treatment in four cases. In squamous-cell carcinoma of the vermilion portion, regional lymph-node metastasis occurred in one of 18 cases (5.56%). Newell[9] observed this complication in 6.3% of his cases. Other authors have reported a higher incidence.

Treatment of primary and metastatic basal-cell carcinoma and squamous-cell carcinoma of the upper lip at this institution is primarily surgical. However, radical neck dissection is usually deferred until there is clinical evidence of metastasis.

Cylindroma of the upper lip is rare. In reviewing the literature from 1927 to 1960, Chaudhry and co-workers[3] found 11 malignant salivary gland tumors of the upper lip, of which six were cylindromas. We found four such lesions. Treatment should consist of wide surgical excision, alone or with irradiation;[3] but, regardless of the method of therapy, recurrences are common. Because of their slow growth, recurrence or metastasis may not become evident for five to 10 years or even longer.[3]

Summary

Of 702 tumors of the upper lip, 38.7% were benign and 61.3% malignant. Of the benign lesions, angiomas and mixed tumors were the most common, comprising 71.3% and 8.83%, respectively, of the total. Of the malignant lesions, basal-cell carcinoma was encountered much more frequently (73.3%) than was squamous-cell carcinoma (23.3%). The latter lesions were distributed as follows: skin 60%, mucocutaneous border 11%, vermilion surface 18%, and mucosa 7%.

Squamous-cell carcinoma of the vermilion portion of the upper lip is rare compared to the frequency with which such lesions are encountered on the lower lip. For each 100 squamous-cell epitheliomas of the lower lip, there was one of the upper lip. The incidence in female patients of carcinoma of the upper lip (22.2%) was higher than that for carcinoma of the lower lip (1% to 3%). The frequency of metastasis and the rate of growth were not found to be any different for squamous-cell carcinoma of the upper lip than for that of the lower lip. However, squamous-cell carcinoma of the mucosa on the under surface of the upper lip had a high incidence of local recurrence.

Of 34 tumors situated in the substance of the upper lip, 22 were mixed tumors and four were cylindromas.

When some men discharge an obligation, you can hear the report for miles around.—Mark Twain

Old Hospitals

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The Fort Crawford Military Hospital at Prairie du Chien, Wisconsin, was under construction during the period August, 1829, to March, 1831, when the post surgeon, Dr. William Beaumont, was conducting most of his classic experiments on the physiology of digestion. The Fort Crawford experiments, fifty-six in number, were probably conducted in the old log hospital which this building replaced. Although stationed at a wilderness outpost with only the most rudimentary facilities, Beaumont used his knowledge of the world literature on gastric physiology and the gastric fistula of his assistant, Alexis St. Martin, to make one of America's greatest contributions to basic medical science.

Fort Crawford Military Hospital

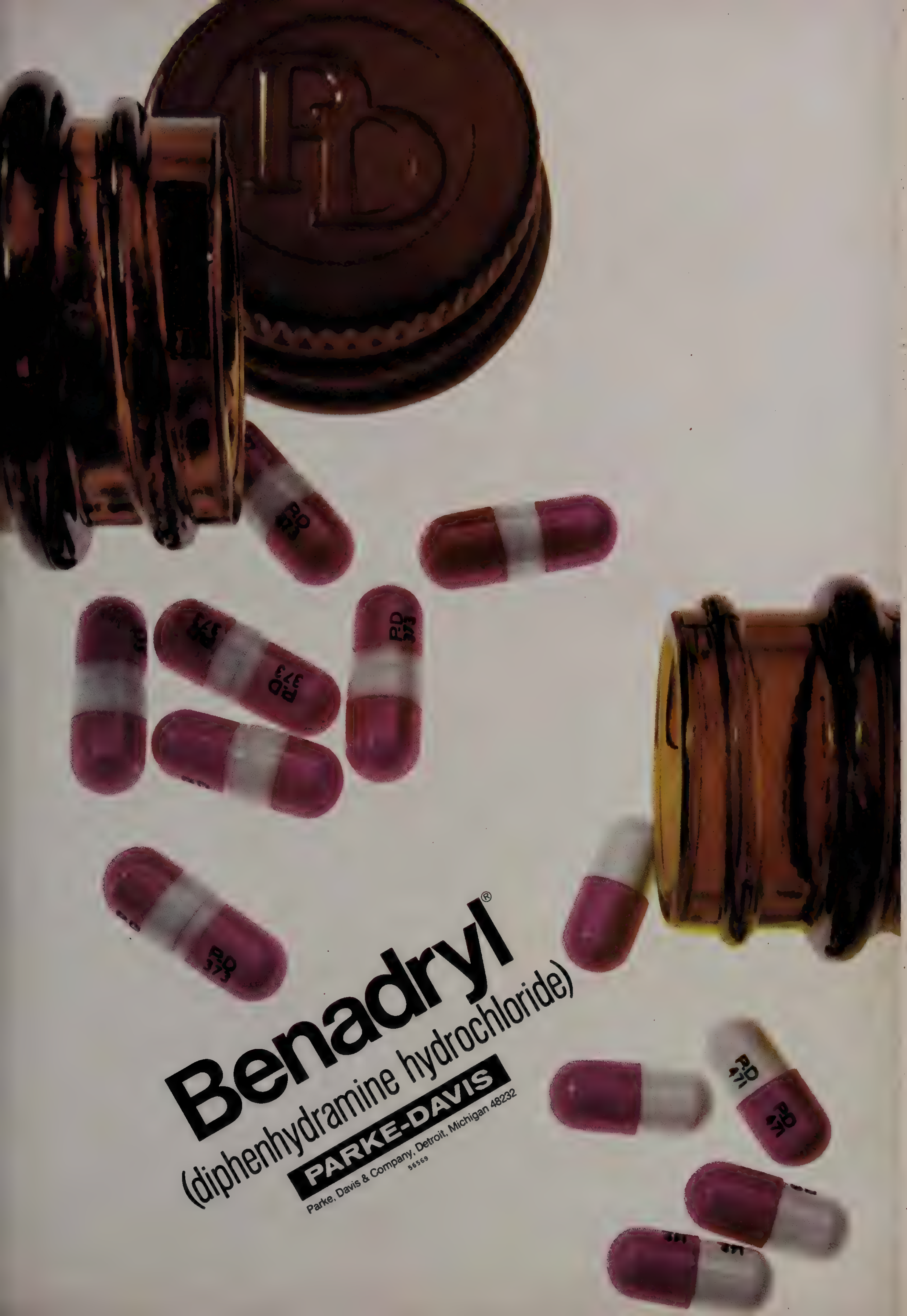
The first eight experiments at Fort Crawford were on gastric temperature and the influence of changes in environmental temperature. The next fifteen were on the accumulation of gastric juice during fasting and under the influence of hunger. Twenty-three experiments compared natural digestion with the *in vitro* effects of gastric juice. The final ten experiments at Fort Crawford were an unsatisfactory series on the effects of bile and pancreatic juice. Beaumont's book, "Experiments and Observations on the Gastric Juice, and the Physiology of Digestion," was published in 1833 at Plattsburgh, New York.

Warren Kump, M.D.
Minneapolis, Minnesota

Ann Med Hist n.s. I, 155, 1929.
Ann Med Hist n.s. V, 28, 1933.

Age

There are people who, like houses, are beautiful in dilapidation.—Logan Smith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Dosage and Administration: *In women:* one 250-mg. oral tablet three times daily for ten days. A vaginal insert of 500 mg. is available for local therapy when desired. When used, one vaginal insert should be placed high in the vaginal vault each day for ten days; concurrently two oral tablets should be taken daily.

In men: When trichomonads are demonstrated, one 250-mg. oral tablet twice daily for ten days in conjunction with treatment of his female partner.

Dosage Forms: Oral tablets–250 mg.
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*Complete list of references on request.

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Editorials

Subtalar Inflammatory Response to Stress

THE CIVILIAN PRACTICE of Orthopedic Surgery includes many patients with low back pain. The symptoms are definite and distressing, but often the physical findings are vague. Treatment is usually conservative, with rest being the keynote. Eventually most of these patients become asymptomatic and are able to return to work, although recovery is sometimes slow.

An interesting parallel is found in military practice. We see an enormous number of young men with painful feet. In the great majority there is a paucity of physical findings. Treatment is usually non-surgical and based on rest. The small minority who fail to respond are eventually discharged from the service.

To be sure, each patient must be carefully and individually evaluated, and generalizations are dangerous. But no one would deny that the possibility of secondary gain is often a factor in persisting complaints. Civilian patients involved in injuries covered by Workmen's Compensation or enmeshed in personal injury litigation may either subconsciously or overtly prolong rehabilitation. Similarly in military life, which for some is neither agreeable nor attractive, a well-placed symptom can result in at least temporary improvement of the environment. A 20-year-old draftee who has done nothing more vigorous than week-end bowling or carrying a sign in a campus demonstration might be expected to have symptoms of foot strain after a ten-mile hike on a hot asphalt road in combat boots with full field gear. Add to his sore feet the prospect of tomorrow's hike, grim at best, and you end up with a man in the dispensary. A day or two of rest and a few aspirin cure 90% of these people.

The patients with persistent pain are eventually more thoroughly evaluated, and orthopedic consultation is obtained. In the majority of these, significant physical findings are absent, x-rays unremarkable, and laboratory tests unrevealing. Rarely are such entities as tarsal coalition, stress fracture, arthritis, infection or tumor found. Therefore most of these cases are diagnosed as foot strain and the treatment remains conservative. Gradually they improve and rarely is complete rehabilitation impossible.

Chambers and Preator* selected patients with symptoms and signs of subtalar inflammation for steroid injection. As an initial and primary method of treatment this approach warrants some discussion. We have all seen individuals involved in sedentary activities for years who develop a painful joint after unusual exertion: the father out for little league football practice, the middle-aged matron after her first jogging, the bank vice-president after the three-legged race at the annual picnic. They come limping into the office with a painful swollen knee, a sore hip limited in internal rotation, or an effused and warm elbow. Treatment for these cases of traumatic synovitis is reassurance, analgesics and rest. Response to this

---

*Chambers, G. H. and Preator, R. F.: Subtalar Inflammatory Response to Stress—A Cause of Foot Pain. Minnesota Med 52: 417, 1969.

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judicious hands-off policy is prompt and gratifying.

Only cases which prove intractable to an adequate period of conservative management are considered for injection therapy. Parenteral steroids and intra-articular injections should seldom be considered for initial therapy in a synovitis due to stress. Violation of a joint with a needle and medication can be associated with complications and should be reserved for patients unresponsive to simple measures. Chambers and Preator obtained excellent results in 19 out of 20 airmen treated by injection; one wonders how a randomly-selected control group treated by rest would have fared.

Michael W. Davis, Major, USA, MC
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APO New York, New York

Significance of Late-Developing Reaction in Allergy Skin Testing

THE DIAGNOSIS of a sensitivity to a specific allergen should correlate with the patient's history and symptoms when exposed to the suspected allergen. Skin testing with allergens continues to be a major diagnostic aid in the diagnosis of allergy. All allergists recognize the limitations of skin testing as presently employed. Their eagerness and enthusiasm for additional methods of detection are ever present.

Similar clinical entities involving the same shock organ, i.e., lungs, nose, skin, are repeatedly observed in patients—with one major difference, however. Some patients present positive skin tests of the immediate type, while others are totally non-reactive. This latter group continues to baffle the physician in the diagnosis and management of allergic disease. At present immunological mechanisms have not been implicated. The recent beta adrenergic theory of atopic abnormality by Szentivanyi[1] offers a plausible explanation for this group of non-reactors.

The interest of Doctors Max Michels and Robert Smith,* in bringing to our attention the presence of these late-developing skin reactions, will surely stimulate further interest. The correlation of these skin reactions with the patient's history, and with symptoms and eosinophilia after nasal challenge is suggestive but not conclusive. The authors' careful discussion in distinguishing these late-developing skin reactions from delayed hypersensitivity should help avoid confusion. To date, their clinical significance remains unclear. Confirmatory evidence in both the basic and the clinical laboratory is needed.

William Sawyer Eisenstadt, M.D.
Minneapolis, Minnesota

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*Michels, Max I. and Smith, Robert E.: Significance of Late-Developing Reactions in Allergy Skin-Testing. Minnesota Med 52:421, 1969.

Reference

1. The Beta Adrenergic Theory of the Atopic Abnormality in Bronchial Asthma. J Allergy 42:203, 1968.

Only he who can see the invisible can do the impossible.—Frank Gaines

Most people should have a coat of arms, inscribed: If not now, when?—Kurt Tucholsky

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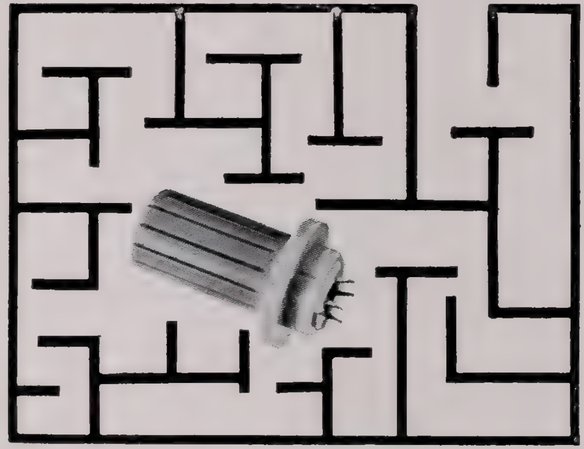

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The Course of the Facial Nerve

THE ANATOMY of the facial nerve is of particular interest and importance.* When facial palsy is present, knowledge of this anatomy permits accurate localization of the pathology. As various portions of the nerve tend to be involved by different types of pathology, localization assists in narrowing the field of diagnostic possibilities and points to further diagnostic steps which might be helpful.

In evaluating facial palsy, the extent of the muscles involved must be determined. Central pathology, proximal to the facial nerve nuclei in the brainstem, results in impairment of the lower face only, sparing the muscles of the eyelids and forehead. Finding all portions of the facial musculature involved (though not necessarily to a uniform extent), if associated with disturbances of the trigeminal nerve, long tracts, or cerebellum, implies pathology at or adjacent to the brainstem. Acoustic neurinoma at the cerebellopontine angle, for example, may produce these findings.

Hearing disturbances often accompany facial palsy. Determination of the type of hearing loss allows further localization. The basic differentiation of sensorineural or conductive loss, as may be done with a tuning fork, may point to involvement either proximal or distal to the geniculate ganglion. Associated eighth nerve lesions involving the segment from the brainstem up to the cochlea often result in specific audiometric abnormalities (markedly impaired understanding of speech, pathological adaption to sound, etc.). Involvement of the cochlea itself results in sound recruitment. Involvement at or adjacent to the middle ear, the "tympanic" (horizontal) segment, is often associated with conductive hearing loss, most commonly by middle-ear disease or by trauma. In these instances otoscopy and the history are of prime importance.

Involvement of the "mastoid portion" (vertical segment) of the facial nerve is most commonly by Bell's Palsy. This is probably basically a problem of localized ischemia and is associated with no other cranial nerve abnormalities. Beyond the stylomastoid foramen, involvement may be of the main trunk or of branches and thus cause regional muscle impairment. In these instances the etiology is most commonly trauma or tumor.

Further localization may be possible based on (1) the exit of the greater petrosal nerve from the geniculate ganglion (employing tear tests), (2) the exit of the nerve to the stapedius muscle (resulting in impaired stapedius muscle function and thus impaired damping of the stapes' excursions, with increased perception of and distress with exposure to loud sounds) and (3) the entrance of the chorda tympani nerve (with accompanying taste and salivation disturbances); but evaluation of these may be more difficult and less reliable.

Thus a knowledge of the course and relationships of the facial nerve allows the localization of its pathologic involvement and facilitates appropriate diagnostic steps and conclusions.

Morton C. Kane, M.D.
Minneapolis, Minnesota

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*Kullmann, G. L. and Cody, D. T. R.: The Anatomy of the Facial Nerve. Minnesota Med 52:213, 1969.

Time

One morning, Andrew Carnegie interviewed two boys for a position. He placed a package in front of each, and told them to start unwrapping. One boy carefully untied the string and placed it in a drawer. The other reached for a pair of scissors, snipped the twine and tossed it into the wastebasket. Carnegie then asked the boys to wait outside.

"Shall I hire the boy who saved the string?" asked his secretary.

"No, I want the other boy," said the steel magnate. "The days of string-saving are over. We're time-savers now."

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Leg Cramps*

The article by Thurn entitled "Treatment of Leg Cramps of Pregnancy with Vitamin B6"*, and the accompanying editorial note in the February issue of *Minnesota Medicine* call for further comment.

The suggestion that an individual in general practice cannot do scientific work without a clinical laboratory is false. Furthermore, the idea of tryptophane loading tests to determine vitamin B6 deficiency, although interesting, is not of importance in substantiating the hypothesis that this agent is of value in the treatment of leg cramps.

Those who watch tooth-paste commercials on television know that the proper experimental design for such a study is a double-blind one. This could easily be done in a general practice setting. A statistically valid difference between drug and placebo groups would provide evidence in support of the hypothesis. An insignificant difference would suggest that the relief of pain was due to psychological or other factors.

The suggestion that other physicians use this treatment in order to provide a larger clinical experience is a poor one since, without a properly controlled study, no meaningful results can be obtained, no matter how many patients are treated.

This lack of proper controls in clinical studies has resulted in many unsettled questions in medicine: for example, the value of long-term anticoagulants in the prevention of recurrence of myocardial infarction.

David A. Berman, M.D.
Minneapolis, Minnesota

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*Thurn, R. J.: Treatment of Leg Cramps of Pregnancy with Vitamin B6. Minnesota Med 52:267, 1969.

Acute Abdominal Emergency*

As the New England Journal of Medicine pointed out recently,[1] Clinical Path Conferences are stimulating to those of us who care for patients even though they may not be as glamorous as presentations in the exciting frontiers of immunology, chromosomal abnormalities, and molecular biology. A case in point is the report of an acute abdominal emergency after gastrectomy beautifully described by Strom in MINNESOTA MEDICINE.* Since a classical education is now so rare we may see more "crur*ae*"† just as we hear a lot about "diverticu*li*."† In reflecting on this case one feels that the recent suggestion[2] about the advisability of exploration with the diagnosis of pancreatitis should be seriously considered. Laparotomy has become remarkably innocuous; the main complication is aspiration pneumonia. If this can be avoided it seems better to make a small incision rather than depend upon blind needle paracentesis which may give intra-luminal bowel content rather than peritoneal fluid.

A recent case of afferent loop obstruction due to volvulus at the gastroenterostomy was seen in our hospital nine years after gastrectomy; the 9-cm. wide duodenum in the right upper quadrant was pierced by the paracentesis

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*Minnesota Medicine 52:319, 1969.

†Tish! Tish! Even the editor and his whole staff, not being students of Latin, missed these grammatical inflections.

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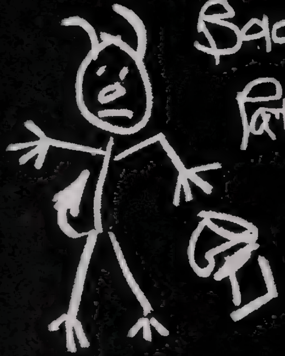

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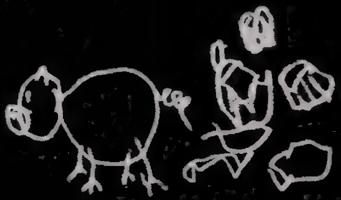

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and the fluid was reported as bile and containing too much amylase to measure accurately.

Another of our patients diagnosed as having pancreatitis who came in drunk with a positive Cullen's[†] and Grey-Turner[†] sign developed pleural effusion after two or three days which on tapping revealed bile.

Laparotomy showed a transected common bile duct as well as disruption of the gastroduodenal artery due to unknown blunt injury. He, like the patient reported in the Clinical Path Conference, died. Thal and Perry[3] maintain that patients who developed signs of pancreatitis after having had gastrectomy should be promptly operated upon.

In all, this was a very stimulating and topical case. Those who continue to prefer gastrectomy to vagotomy and pyloroplasty, in the management of the complications of duodenal ulcer, have to answer for the higher immediate mortality and the severity of those complications, such as problems with the afferent loop or complications of marginal ulceration which occasionally develop even many years later.

Raymond C. Reed, M.D.[*]
Little Rock, Arkansas

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[*] Professor of Surgery, Veterans Hospital.
[†] See Test Your Word Score Page 933.

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1. New Eng J Medicine 280:384, 1969.
2. Lataste, J.: Early Surgical Intervention in Acute Pancreatitis. Presse Med 74:1875, 1966.
3. Ann Surg 143:266, 1958.

Test Your Word Score

Ameloblastoma—*a neoplasm originating from enamel origin* (page 899).

Eponymic—*an adjective derived from a prominent proper name, e.g., cesarean from Caesar* (page 903).

Bouginage—*treatment of the interior of a canal by passage of a bougie* (page 912).

Keratoacanthoma—*a papular lesion, usually on the face, having a crater filled with a keratin plug and growing rapidly to maximum size, then resolving spontaneously* (page 916).

Neurilemmoma—*a tumor of the peripheral nerve sheath; a schwannoma* (page 917).

Cullen's Sign—*Periumbilical darkening suggesting intraperitoneal hemorrhage* (page 933).

Grey-Turner's Sign—*Areas of pigmentation about umbilicus and loins suggesting acute hemorrhagic pancreatitis* (page 933).

Feulgan (test)—*developing a red color by hydrolyzing with HCl solution and treating with 1 percent decolorized rosaniline solution* (page 1000).

Tomography—*Curvilinear motion of x-ray tube synchronous with a moving plate causing the selected plane to remain stationary* (page 1001)

Hypercapnia—*excess of carbon dioxide in the blood* (page 1029).

Oximetry—*determination of the oxygen saturation of arterial blood by means of bichromate photo-electric colorimetry* (page 1031).

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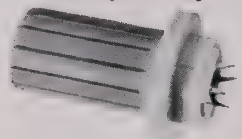

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The Editor's Soliloquy

Litigation Disease

To listen to court testimony regarding an accident, the average undiscriminating person might well conclude that nearly any disease or disability can potentially result from an accident. Plaintiffs' attorneys have astutely garnered from their clients' experiences an exhaustive list of ailments and complaints from A to Zed—as possible if not probable sequels of an accident.

"After all, there is nothing to lose!" Why not incriminate an accident for that headache, that crick in the neck, that twinge in the back, that you-name-it, that mysteriously appears sometime *after* an accident in the victim who was "never subject to previous headaches, cricks, or twinges!"

Unfortunately, "qualified and expert" testimony has "established" that a remote three-to-four-year-old non-organic strain, without bruise, fracture, laceration or muscle rupture, has "caused" obvious new disease or "contributed" to pre-existing disease.

The fallacy: *post hoc; ergo propter hoc** dies a hard death; it has persistently plagued logicians down the centuries and is still accepted by the untutored and exploited by the unscrupulous. Consecutiveness *per se* does not imply causality and should never constitute a basis for sound medical doctrine.

Neither incidents nor accidents cause disease. If an injury has been sustained, the victim will suffer the effects of that injury immediately; on the other hand, any injury which does not cause immediate distress is indeed a minor one and represents nothing more serious than a non-organic strain, comparable to what any athlete might experience after strenuous activity. Such discomfort is physiologic, not organic.

Even if the injury is severe enough to cause organic damage (a fracture, muscle rupture, ligament tear, skin laceration), these damages heal in a more or less scheduled period of time. When healing is complete most of the sequelae of that injury are terminated. The chapter on that incident is closed!

Litigation disease has its obvious etiology: the history relates an incident, usually referred to as an injury, and subjective symptoms referable to almost any extant set of symptoms or disease; the physical findings are irrelevant, the treatment is immaterial, and the prognosis is contingent upon the outcome of the pending lawsuit or its settlement.

Litigation disease is not catalogued in medical annals; but it does exist.

Carl O. Rice, M.D.

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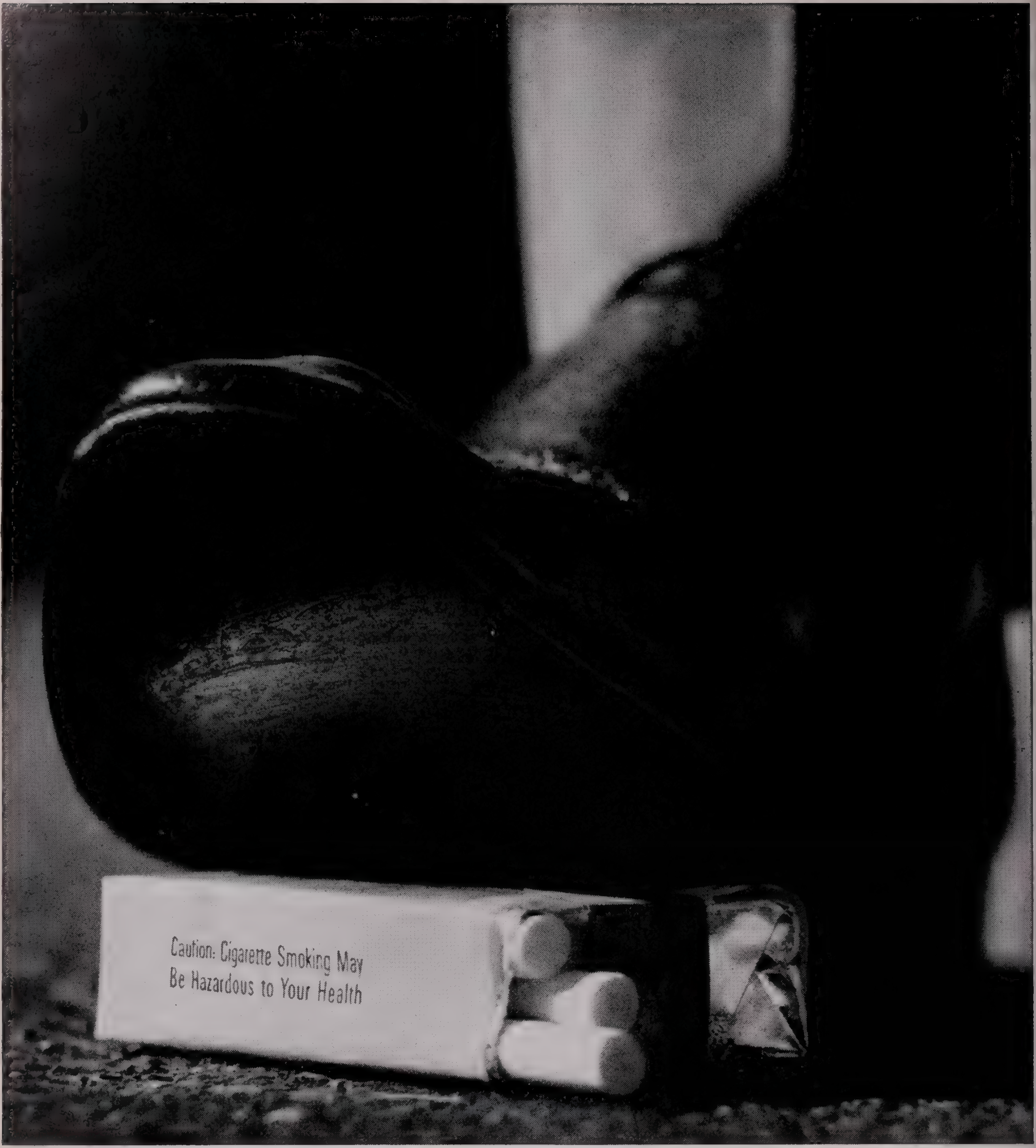
*After this; therefore on account of this.

* * *

Old Doc Hess says: If you do not want your autographed picture to be relegated to the hidden file, frame it, attach the hanging hook, the nail to hang it on and the hammer to pound the nail.—C.O.R.

* * *

Busy souls have no time to be busybodies.—Austin O'Malley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MINNESOTA MEDICINE

HONOR AWARD

Minnesota Medicine Medical Writing Awards, 1969

It is with pleasure that the Board of Editors announces the winners of the eighth annual Minnesota Medicine Medical Writing Awards chosen from articles published in Minnesota Medicine during the year of 1968.

First place plaques were awarded by Dr. Carl Rice during the annual meeting of the Minnesota State Medical Association in Minneapolis at the New Members, County Officers and Delegates Dinner to Donlin M. Long, M.D.; Shelley N. Chou, M.D. and Lyle A. French, M.D., for their article "Evaluation and Treatment of Hydrocephalus"; and to Yoshio Sako, M.D. and Martin L. Beard for their article "Coarctation of the Aorta in Veterans", which appeared in the June, 1968, issue of Minnesota Medicine.

Certificates for excellence in medical writing were awarded to the authors whose articles were felt to be particularly outstanding by the Board of Editors. These authors are listed on page 939.

Laboratory Letter

The trouble with urinary steroid tests is that so many variables, other than endocrine disorders, influence results. Among these are: completeness of urine collection; stress; age and sex; varying excretion rate of steroids during the day; and interfering substances such as drugs.

In theory at least, you can control most of these variables. You place the patient in the hospital, instruct nurses to collect all urine for 24 hours, and hope the hospital atmosphere doesn't cause too much stress. The 24-hour collection period helps assure you of an adequate specimen and gets you around the diurnal variation problem: 17-ketosteroid values peak in the morning, vary during the day, and dip during sleep. Besides this normal shifting, emotions and physical activity can change results. Still, in ambulatory patients and in some hospital patients, you can't be sure of basal conditions.

Age and sex pose less of a problem. Once you get your results, you refer to normal ranges for age and sex (Table 1), and you keep in mind that in women, 17-ketosteroids roughly measure androgenic activity. You know that in women the adrenals are the source of almost all 17-ketosteroids, while in men the adrenals account for only two thirds. The testes supply the other third. And you appreciate that in both sexes 17-ketogenic steroids are a better measure of adrenal activity than 17-ketosteroids.

TABLE I

Normal Values For Urinary Steroids

	Age-yrs.	Men	Women
17-Ketosteroids	2-5	Less than 2 mg./24 hrs.	Less than 2 mg./24 hrs.
	5-10	3-6 mg./24 hrs.	3-6 mg./24 hrs.
	10-15	6-15 mg./24 hrs.	5-11 mg./24 hrs.
	15-60	10-20 mg./24 hrs.	5-15 mg./24 hrs.
	60-90	5-20 mg./24 hrs.	3-13 mg./24 hrs.
17-Ketogenic Steroids	Under 1 yr	Less than 1.0 mg/24 hr.	Less than 1.0 mg/24 hrs.
	2-5	1-5 mg/24 hrs.	1-5 mg/24 hrs.
	5-10	2-9 mg/24 hrs.	2-9 mg/24 hrs.
	20-50	11-22 mg/24 hrs.	7-18 mg/24 hrs.
	Over 50	4-14 mg/24 hrs.	2-10 mg/24 hrs.

Drugs? Well, you try to keep them from interfering with the tests by stopping all medications 48 hours before the urine collection. But, human nature being what it is, some patients forget and others don't always follow instructions to the letter. As a consequence, you may get puzzling drug-induced results. If this should happen, you may want to consult this table.

TABLE 2

Drug	17-Ketosteroids	17-Ketogenic steroids
1. Meprobamate, Triacetyloeandomycine, Spirolactone, Phenaglycodal (Ultran), Penicillin, and Nalidixic Acid (NegGram)	increases	increases
2. Chlordizepoxide hydrochloride (Librium), and Etryptamine acetate (Monase)	decreases	increases
3. Chlorpromazine (Thorazine)	increases	decreases
4. Hydroxysine (Atarax)	no effect	increases
5. Ethinmamate (Valmid)	increases	no effect
6. Reserpine	decreases	decreases

Richard L. Reece, M.D.
Minneapolis, Minnesota

The
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1969

Authors	*Manuscript*	*1968 Issue*
David E. Dines, M.D.; William W. Douglas, M.D. and Edward C. Rosenow, III, M.D. Rochester, Minnesota	Blood Gas Monitoring of Patients in Respiratory Failure	December
Donald B. Effler, M.D. Cleveland, Ohio	Myocardial Revascularization with Internal Mammary Artery Implants	August
William A. Hawk, M.D.; Frank L. Weakley, M.D. and Rupert B. Turnbull, Jr., M.D. Cleveland, Ohio	Some Important Colonic and Rectal Polyps	August

Minnesota Medicine is honored to have this opportunity to acknowledge the work of its distinguished authors and to express to them applause, thanks and cordial best wishes.

Board of Editors

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ABOUT
THE WEAKER
SEX?

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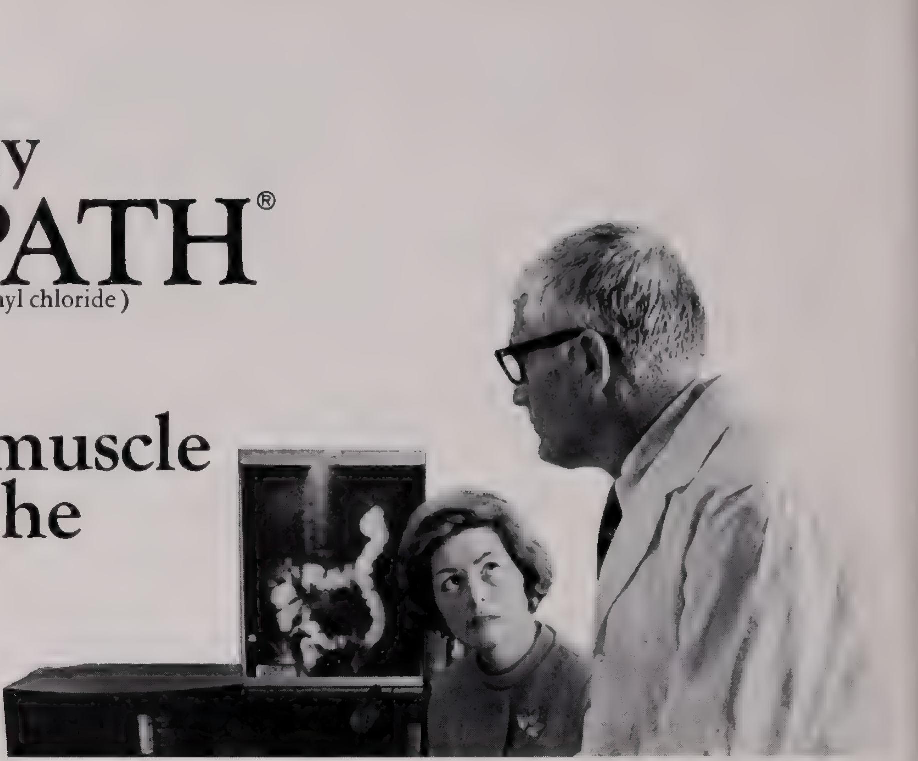

Usual Adult Dosage

One 'Milpath'-400 tablet, three times a day at mealtimes, and two at bedtime. For greater anticholinergic effect, two 'Milpath'-200 tablets, three times a day at mealtimes and two at bedtime. Doses of meprobamate above 2400 mg. daily not recommended.

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Useful in organic and functional disorders with hypersecretion and hypermotility of G.I. tract, especially when accompanied by anxiety, neurosis, or tension states. Should be used as an adjunct to all other therapeutic measures.

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Tridihexethyl chloride: Urinary bladder-neck obstructions, e.g., prostatic obstruction due to hypertrophy; pyloric obstructions because of reduced motility and tonus: organic cardiospasm (megaesophagus); glaucoma; possibly in stenosing gastric or duodenal ulcers with significant gastric retention.

Meprobamate: Previous allergic or idiosyncratic reactions to meprobamate.

Precautions

Tridihexethyl chloride: Use cautiously in elderly males (possible prostatic hypertrophy).

Meprobamate: Carefully supervise dose and amounts prescribed. Consider possible dependence or habituation (reported occasionally after excessive use), particularly in severe psychoneurotics, alcoholics, ex-addicts. Withdraw gradually (one or two weeks) after excessive dosage for weeks or months to avoid recurrence of pre-existing symptoms (e.g., anxiety, anorexia, insomnia) or withdrawal reactions (e.g., vomiting, ataxia, tremors, muscle twitching; rarely, epileptiform seizures, more likely in those with CNS damage or latent convulsive disorders). If drowsiness or visual disturbance occurs, reduce dose and advise against activity requiring alertness (driving, machinery operation). Effects of excess alcohol may be increased. Grand mal seizures possible in persons with both petit and grand mal. Prescribe cautiously in small amounts to patients with suicidal tendencies. Prescribe with caution to patients with known sensitivity to compounds of similar chemical structure, e.g., carisoprodol.

Side Effects

The following side effects of components may occur with 'Milpath'.

Tridihexethyl chloride: Severe effects rare on recommended dosage. Anticholinergic effects: dry mouth (fairly frequent at oral doses of 100 mg.), constipation or "bloated" feeling. Possible: tachycardia, dilation of pupils, increased ocular tension, weakness, nausea, vomiting, headache, drowsiness, urinary hesitancy or retention, dizziness.

Meprobamate: Drowsiness, sometimes with ataxia, usually controlled by decreasing dosage, occasionally with aid of central stimulants (e.g., amphetamine). Rarely, allergic or idiosyncratic reactions (usually after one to four doses); in mild form: itchy, urticarial or erythematous, maculopapular rash, generalized or confined to groin. Acute nonthrombocytopenic purpura with cutaneous petechiae, ecchymoses, peripheral edema and fever, transient leukopenia, and one fatal bullous dermatitis (after meprobamate and prednisolone) reported. More severe, very rare hypersensitivity: fever, chills, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (one fatal), anuria, anaphylaxis, stomatitis and proctitis. Treat symptomatically (e.g., epinephrine, antihistamines, possibly hydrocortisone); stop and do not restart the drug. Isolated agranulocytosis, thrombocytopenic purpura, one fatal aplastic anemia reported, but only in presence of known toxic drugs, porphyric symptoms reported but relationship not established. Fast EEG activity, usually after excessive dosage. Impairment of visual accommodation reported by one observer. Fixed drug eruption with meprobamate and cross reaction to carisoprodol reported.

Suicidal attempts may produce drowsiness, lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse, and death. Excessive dosage has led rapidly to sleep, then reduction of vital signs to basal levels. Empty stomach, and if respiration becomes very shallow and slow, cautiously give CNS stimulants (e.g., caffeine, pentylenetetrazol, amphetamine); also pressor amines if indicated.

Supplied

In two strengths:

'Milpath'-400: Yellow, scored tablets.

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Before prescribing, consult package circular.

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(1928A01J)

The Viewing Box

Severe Generalized Abdominal Pain

This 28-year-old lady was admitted with the complaint of sudden onset of severe generalized abdominal pain, worse in the left flank and radiating to both shoulders on lying down. This was accompanied by vomiting and faintness. Her last normal menstrual period was seven weeks prior to admission. Physical examination revealed a pale woman with blood pressure 90/60, pulse 140. Her abdomen was flaccid but tender. This tenderness was greatest in the L.L.Q. and hypogastric regions. Pelvic examination showed pain on motion of the cervix and fullness in the pouch of Douglas. The uterus was slightly enlarged. No adenexal mass was palpable. A supine film of the abdomen was made (Figure 1).

What is your diagnosis? (See next page.)

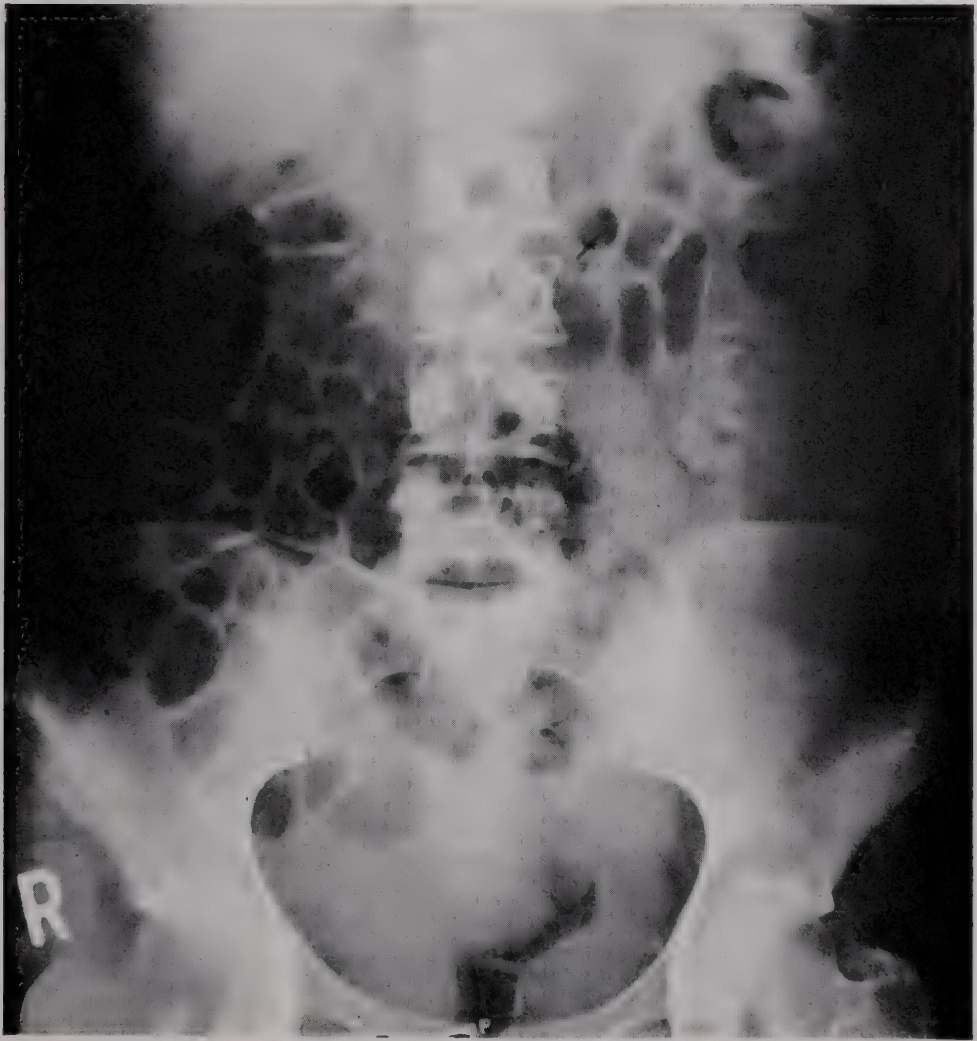

Figure 1

Diagnosis: Ruptured ectopic pregnancy with secondary hemotoperitoneum.

We are all acutely aware of the extreme importance of recognizing the presence or absence of intraperitoneal fluid or blood, whether caused by trauma or acute or chronic disease processes. There are several well recognized roentgenologic signs of free intraperitoneal fluid which will increase our diagnostic acumen in this area. These are the "dog's ears sign," "flank stripe" and obliteration of the hepatic angle (Figure 2).

These signs are best evaluated on supine films of the abdomen using a low kilovoltage technique. The first of these is the "dog's ears sign" of fluid in the pelvic recess. The pouch of Douglas and peritoneal recesses on each side of the rectum and bladder are the lowest portions of the peritoneal cavity and tend to fill with fluid first. This fluid extends superiorly above the bladder and resembles the projecting ears of a dog. As the amount of fluid increases, it

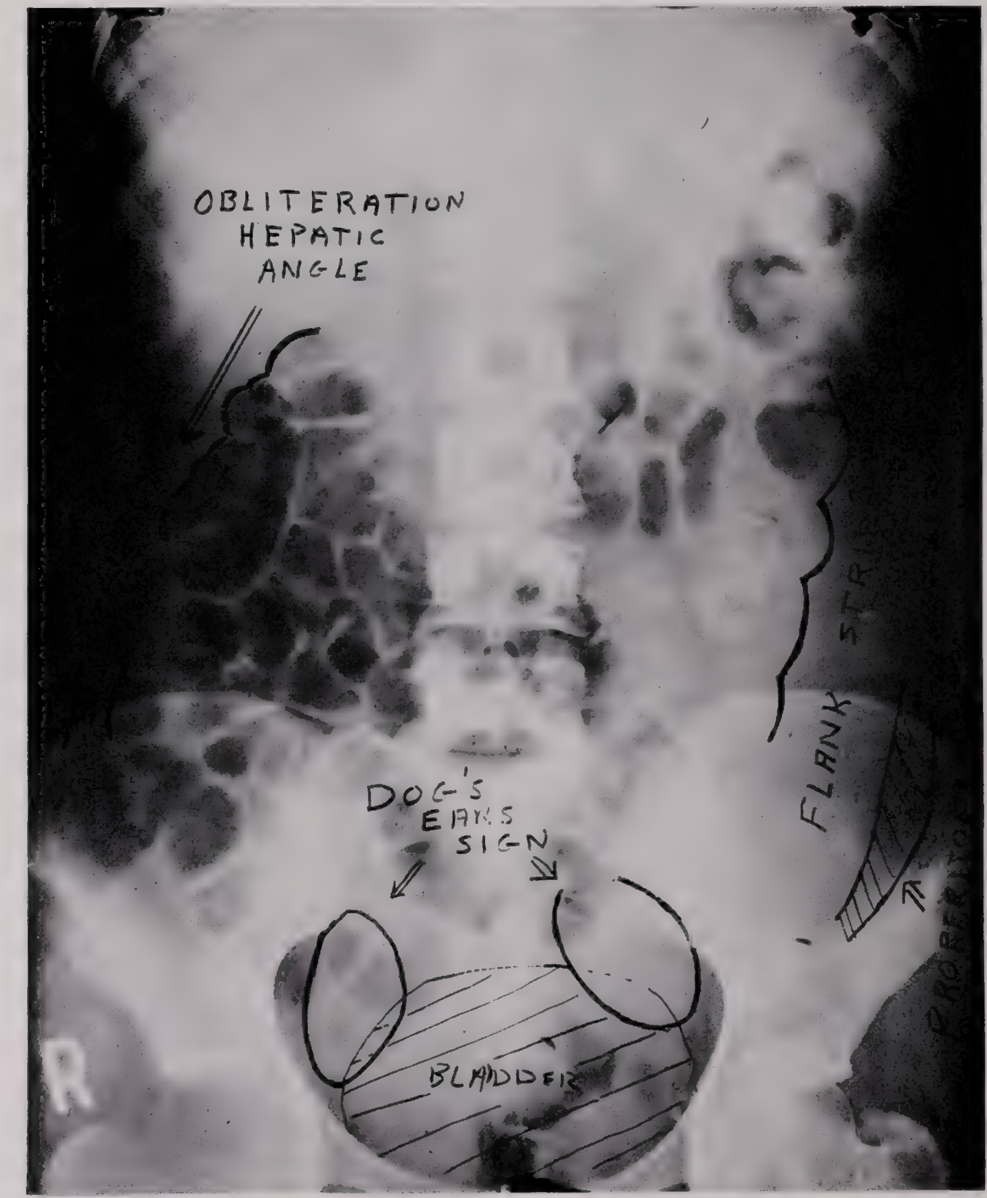

Figure 2

spills out into the flanks and causes flattening of the haustra and displacement of the colon medially away from the extraperitoneal or properitoneal fat line, giving us our second sign—the "flank stripe." One thousand cc. of free fluid should produce a definite stripe.[1] The properitoneal fat line is that lucent line seen on plain film which lies between the peritoneum and transverse abdominal muscle. The colon normally lies within 2 mm. of this line.

The last sign is the obliteration of the hepatic angle. The lower right lateral margin of the liver is normally clearly seen because of the large quantity of omental fat contiguous with the liver at this point. When fluid is sufficient to reach this area it insinuates itself between these structures, obliterating the hepatic angle.

Margulies[2] feels that both the flank stripe and the hepatic angle are excellent signs in assisting us in the evaluation of the presence or absence of free fluid and that many of the difficulties encountered can be avoided by studying the right flank in the region of the hepatic angle. It must be remembered that fluid-filled small bowel may occasionally interpose itself between the descending colon and properitoneal fat line, giving us a false flank strip on the left. The site of trauma, the site of acute disease process and the position of the patient after injury or onset of the disease process influence the location of free fluid.

The roentgenogram used in this article shows all three signs. At surgery the patient was found to have 1500 cc. of free blood.

Douglas B. Ketcham, M.D.*
Minneapolis, Minnesota

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*Department of Radiology, University of Minnesota and Hennepin County General Hospital.

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Automation and Medicine

Since the practice of medicine is essentially the computation of statistical probabilities I think there is little doubt that if all relevant information were stored in one place and made available for computation the accuracy and hence the quality of medical care would be greatly improved. . . . The seasoned clinician enlarges his knowledge and improves his statistical calculations as he grows older . . . but most of his acquired information dies with him. The computer remains immortal.

This development will not encroach upon the time-honored duties and values of the physician . . . but he will be forced to think quantitatively about the information he obtains. This in itself will greatly increase the value of clinical data and will heighten the perceptions and analytical ability of the physician . . . his personality will remain a deciding factor in the therapeutic process, but he will no longer be forced to call upon his own memory for the complex assessment of the statistical probabilities of each diagnosis. . . . Fortified with the vast knowledge of a computer he will more fully develop his own potential as a physician and as a human being.*

---

*M. Henry Williams, Jr., as quoted in Richard Magraw: Ferment in Medicine, 1, 1966.

Book Reviews

The true University of these days is a Collection of Books.—Carlyle

WATER AND ELECTROLYTE METABOLISM AND ACID-BASE BALANCE. By Edward Muntwyler, Ph.D. C. V. Mosby Company, St. Louis, 1968. Price: $5.85.

This paper-bound handbook has 143 pages of text, a useful set of 311 references and a reasonably usable index.

It is divided into three sections, the first covering water and electrolyte metabolism as a general foundation of the basic physiologic processes. This, as well as the second section covering the basic physiology of acid-base balance, make up an excellent review so that the physician can much better understand problems to be dealt with. A very helpful summary of the Brønsted-Lowry concept of the source of hydrogen ions and their disposition can be found on pages 59 to 65.

The third section on correction of fluid, electrolyte, and acid-base balance disturbances is primarily designed for the internist or those dealing with non-surgical problems. There is actually very little coverage of the rather wide variety of distorted conditions that the surgeon deals with, such as the translocation of fluids and electrolytes in massive infectious processes, the mixed metabolic and respiratory problems, and those of excessive drainages of various body secretions and excretions.

This booklet should be quite useful, therefore, as a review of the general subject of water and electrolyte metabolism and acid-base balance and chemistry of blood gases. For the practicing physician, this booklet is particularly pertinent. It should also be useful as an examination review.

J. H. Strickler, M.D.
Minneapolis, Minnesota

RADIOACTIVE NUCLIDES IN MEDICINE AND BIOLOGY. Volume II, Third Edition. Author—Solomon Silver. Publishers—Lea and Febiger.

The third edition of this book was timely because of the significant advances in nuclear medicine since the previous edition which was published in 1962. The present volume contains 539 pages which is over 200 pages more than in the second edition. The first half of the book deals with the thyroid gland so that it represents a complete monograph on this subject. There is more detail on the evaluation and treatment of thyroid than is probably needed for most nuclear medicine clinics and reflects the primary interests of the author.

This volume contains several chapters which were not present in the previous edition. These chapters relate to scanning, measurements of blood flow and renal function. Sufficient detail is included on these subjects to make them adequate for most readers who are involved in the practice of nuclear medicine.

No consideration is given in this book to the advances in nuclear instrumentation and recent developments in radiopharmaceuticals. It is assumed that these subjects will be covered in detail in the third edition of Volume I, which is yet to be published.

The list price of this book at $12.50 makes it very competitive with several other books on the market dealing with advances in nuclear medicine.

Merle K. Loken, M.D., Ph.D.
Minneapolis, Minnesota

SURGERY OF THE ADRENAL GLANDS. By Lawrence W. O'Neal, C. V. Mosby Company. Price: $19.50.

This book is intended primarily for use by surgeons and contains contributions by nine internists, surgeons, anesthesiologists, radiologists, endocrinologists and pediatricians, all from St. Louis, Missouri. Although the principal author, Lawrence W. O'Neal, states that "the sheer volume of available information and its complexity are somewhat intimidating to the clinician," this volume contains in 286 pages a wealth of well organized material which should be of great value to every surgeon and clinician interested in this field. After discussion of embryology and anatomy of the adrenal glands, the biosynthesis, metabolism, physiology and function of adrenal hormones are discussed in depth. There are chapters on the commonly-found tumors of the adrenal glands, an excellent outline on sympathetic tumors and, in a different chapter, on pheochromocytoma, Primary aldosteronism, Cushing's syndrome, as well as virilizing and feminizing states, are treated in different chapters. A chapter devoted to adrenalectomy for carcinoma of the breast also contains abundant information on other endocrine ablative surgery as well as on chemotherapy. The chapter on roentgenology of the adrenal glands is unique and superb. Here one finds excellent film reproductions, for example of adrenal arteriograms, ACTH-producing lung cancers, or dental films showing the loss of lamina dura in Cushing's disease.

I wish the author had included a review of the recent history of discoveries in the field of adrenal surgery and physiology, and also an opinion concerning adrenalectomy for hypertension of undetermined origin, which is in my opinion still an unsettled problem.

H. W. Heupel, M.D., Ph.D.
Minneapolis, Minnesota

Fracture Conference

Fracture of the Os Calcis*

Dr. Edward D. Henderson:† We have an interesting problem to present this morning.

Dr. Richard T. Chiroff:‡ A 56-year-old white housewife fell off a ladder, a distance of approximately eight feet. After the fall, she complained of pain in the left foot, particularly in the heel, and was unable to bear weight on it. She was brought to the hospital where examination revealed swelling and ecchymosis over the entire left foot below the ankle. The neurovascular status of the distal portion of the foot was normal. She complained of some low back pain as well, but the neurologic examination revealed nothing abnormal. Roentgenograms of the lumbosacral part of the spinal column were normal.

Dr. Henderson: Dr. Boyce, what kind of a fracture is this?

Dr. Daniel Boyce:# It is a fracture through the calcaneus, and I think it involves the subastragalar joint (Figure 1).

Dr. George Simons:‡ This is certainly a comminuted fracture of the os calcis.

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*Fracture conference held June 24, 1968.

†Consultant in Orthopedic Surgery, Mayo Clinic and Associate Professor of Clinical Orthopedic Surgery, Mayo Graduate School of Medicine, University of Minnesota, Rochester.

‡Resident in Orthopedic Surgery, Mayo Graduate School of Medicine, University of Minnesota, Rochester.

#Associate Consultant, Section of Orthopedic Surgery, Mayo Clinic, Rochester.

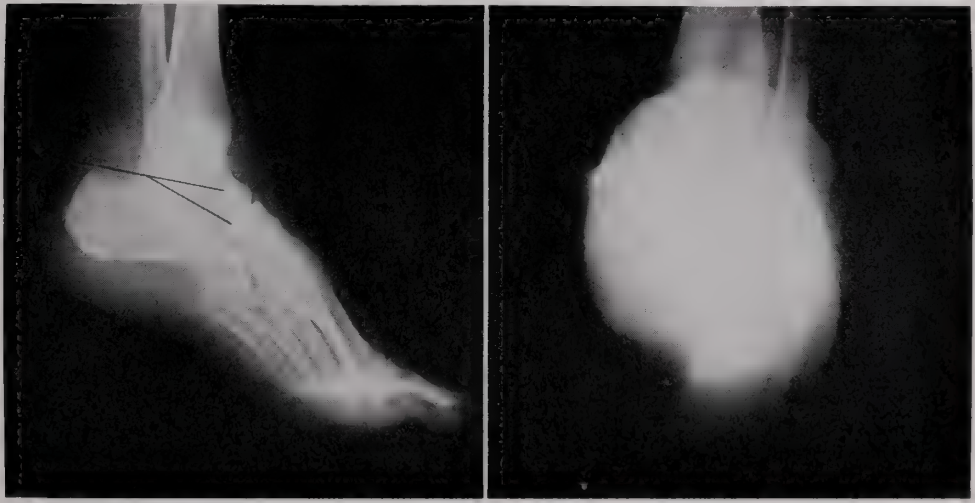

Fig. 1—At admission. (Left) Lateral view of left foot, showing loss of tuber joint angle (20 degrees) and marked comminution of fractured os calcis with involvement of subtalar joint. (Right) Tangential view of fractured left os calcis, showing lateral "spread" of bone and more or less intact medial cortex with single fracture line.

Dr. Henderson: How would you tell whether it went into the subtalar joint?

Dr. Simons: The right tuber joint angle appears somewhat reduced. I would say it is probably five or 10 degrees less than it should be. Also, one might take other films to show the fracture better.

Dr. Henderson: This is a type 6 Watson-Jones fracture—a comminuted fracture through the entire body of the os calcis with loss of tuber angle. These are the two aspects of fractures of the os calcis that make them difficult to treat. There are many methods of treatment, all the way from putting on a well-padded cast and allowing the patient to walk on it, to various types of open reduction with or without bone grafting, to triple arthrodesis, to primary subastragalar arthrodesis. There are also many methods of closed reduction with or without insertion of Steinmann pins. The reason I bring this up is that Dr. McReynolds has reported a series of cases in which he has done open reduction of these fractures.

He pointed out two principles. The first is that almost all the comminution of these fractures of the os calcis is on the lateral side, while on the medial side there is usually just one fracture line. This is important. Most surgical procedures for open reduction approach the os calcis from the lateral side and attempt to piece the fragments together and compensate for the compressed cancellous bone by insertion of bone grafts. Dr. McReynolds pointed out that on the medial side there is a practically intact, solid wall of the os calcis with just one fracture line through it.

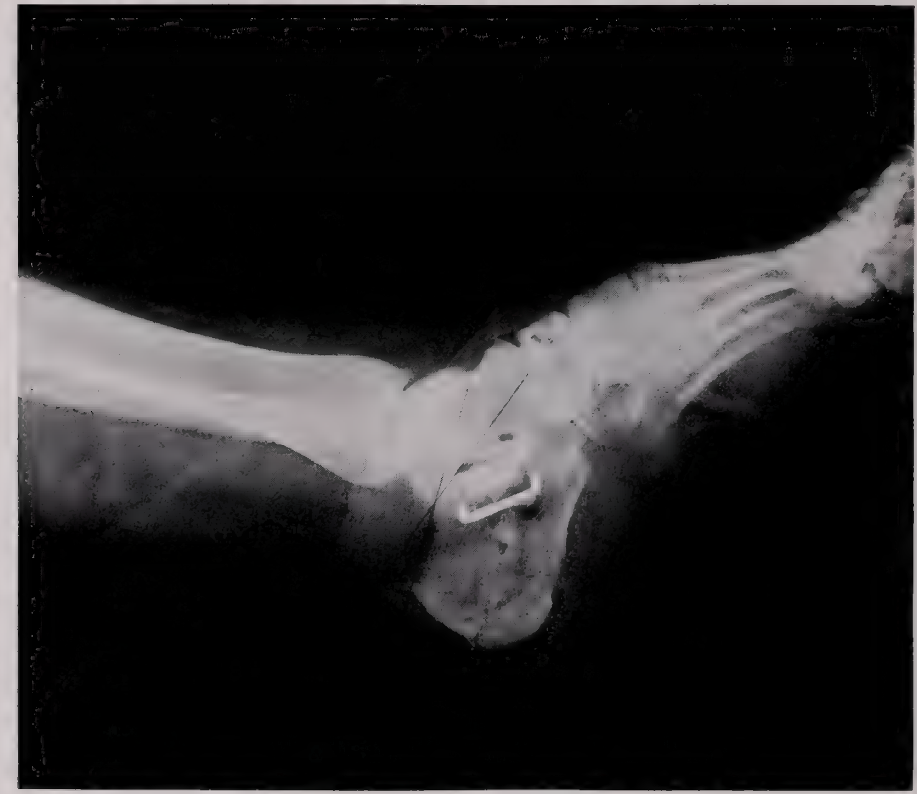

Fig. 2—Lateral view of fractured left os calcis at time of open reduction via medial approach and fixation with one Vitallium staple. Tuber joint angle is now 25 degrees.

His second point is that the os calcis is made wider by the fracturing force. This increased width causes the calcaneus to impinge on the peroneal tendons and on the malleoli and is the cause of some, if not all, of the postfracture symptoms these patients have. You can see on the roentgenograms that the lateral displacement on the anteroposterior view is moderate. You can also see that it is on the lateral side. If you look closely, and are thinking about it, you can see that the medial cortex of the os calcis is relatively intact and not comminuted.

We used Dr. McReynolds' method of open reduction on this fracture (Figure 2). It is absolutely essential that the approach be made from the medial side, so that you can see the medial side of the os calcis and rather easily reduce the fracture and then hold it with one or two staples. In this case it was held with one staple. The tuber angle has been almost completely corrected; then, after the reduction of the fracture, manual compression of the sides of the os calcis reduced the explosion-type enlargement of the lateral side of the calcaneus.

Dr. Chiroff: Thirteen days after the operation described by Dr. Henderson, the extremity was placed in a short-leg cast and the patient was allowed up on crutches without weight bearing.

Dr. William H. Bickel:* How do you hold the fracture while you are doing the internal fixation?

Dr. Henderson: It is fairly easy to do by using some type of a pry.

Dr. Bickel: The Steinmann pin is not used in the os calcis?

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*Consultant, Section of Orthopedic Surgery, Mayo Clinic, Rochester.

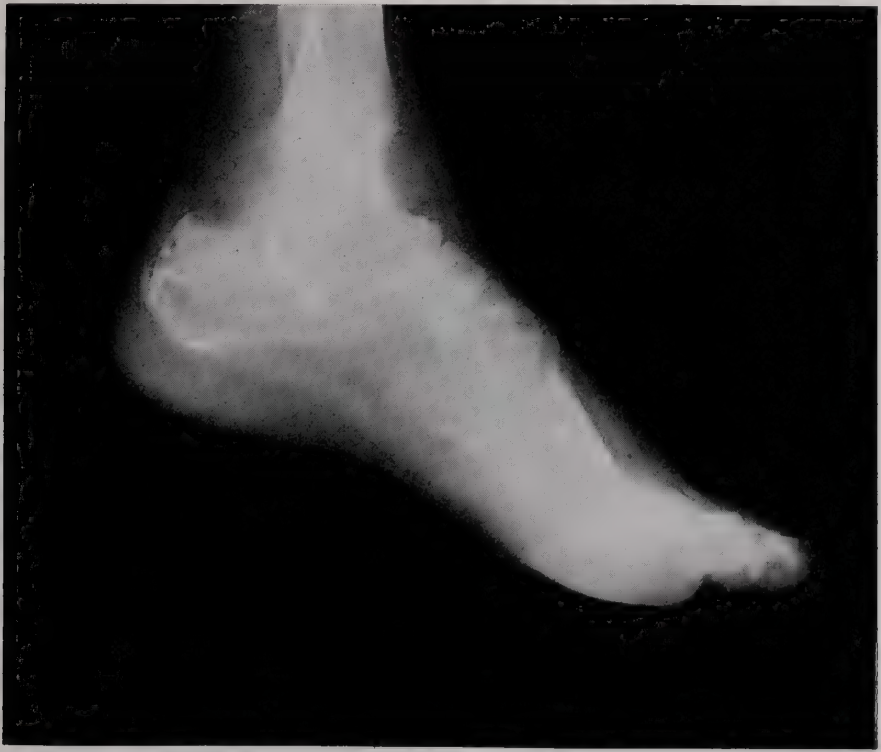

Fig. 3—Lateral view four months postoperatively. Patient was free of pain and had no swelling of foot even after walking all day.

Dr. Henderson: No. The advantage of the medial-side approach is that you have an intact cortex which you can lever into position and which is stable, once reduced and fixed with the staple.

Dr. Chiroff: The patient was allowed to start weight-bearing 13 days postoperatively. Four months after injury, roentgenograms showed good union of the fracture (Figure 3). She was seen here for follow-up examination again at six months after the injury (Figure 4).

Dr. Henderson: At the time I last saw this patient, she was walking without pain. She was still not able to walk on her toes satisfactorily, but she had a full range of motion in her ankle joint. There was about 10 or 15 degrees of motion at the subastragalar joint and this was painless. I anticipate that within the next few weeks or months she will be able to walk on her toes. She has no swelling in her foot.

Dr. McReynolds has now operated on 11 heels in nine patients and has used a bone graft in only one. The only problem in the medial approach is to retract the neurovascular bundle and to avoid the cutaneous nerve that runs down the medial side of the heel. When he approaches the heel on the medial side, he pries the fragment into position and then compresses the heel laterally. He usually uses just one staple but sometimes needs two. He applies a walking, short-leg cast approximately two weeks postoperatively and allows full weight-bearing, with immobilization for about six weeks.

Of these 11 heels, one required a subastragalar arthrodesis. In another there was so much comminution that Dr. McReynolds did a bone graft; but he thinks now that this was not necessary. The average loss of the tuber angle was only 11 degrees, and all nine patients returned to work. The only complication is that the patients do not have normal subastragalar motion (I do not think we could expect this).

I have been doing open reductions on minimal-displacement fractures of the os calcis from the lateral side, but apparently it is a much more extensive

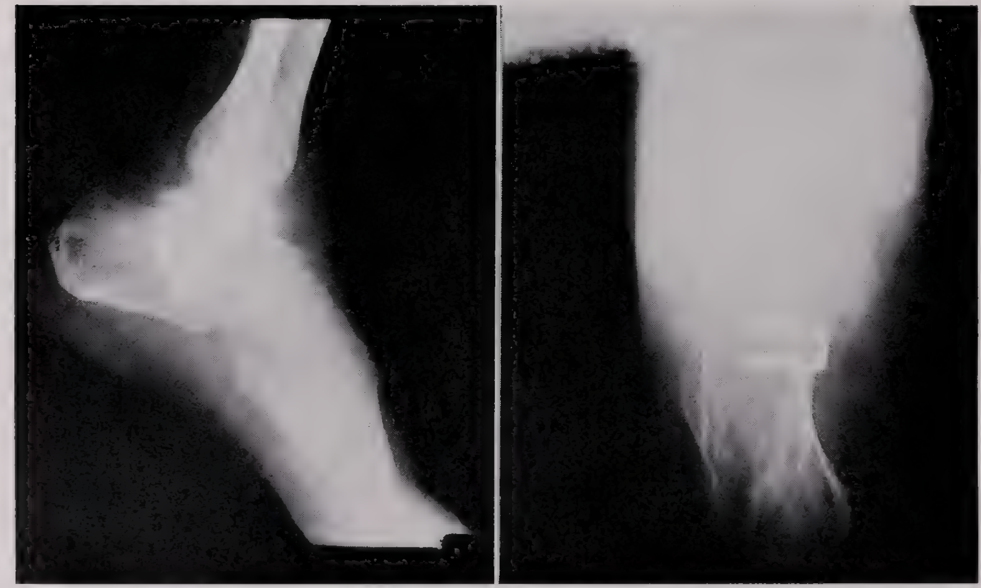

Fig. 4—At six months postoperatively. (Left) Lateral view shows tuber joint angle of 30 degrees. Patient continues to be free of pain. There is approximately 15 degrees of motion in subtalar joint. (Right) Tangential view shows excellent reestablishment of contour of bone.

operative procedure than the one described by Dr. McReynolds. The other advantage to his method is that you get good secure fixation, you can apply a walking cast, and the patients do not get the disuse osteoporosis we see in many patients treated by the other methods.

Dr. Paul R. Lipscomb:* Do you retract the neurovascular bundle superiorly or inferiorly?

Dr. Henderson: Superiorly. Dr. McReynolds makes the incision inferior to the neurovascular bundle.

Dr. Bickel: Did he think there was ever a necessity for opening laterally to put a big fragment back, one that he could not reduce from the medial side?

Dr. Henderson:

In the cases which he reported this was not necessary, but he apparently manipulates or compresses them rather vigorously; waits a few days for the swelling to subside; then casts the foot with the ankle in neutral position, and starts weight-bearing in two to three weeks.

Dr. Mark Coventry:†

I heard and enjoyed Dr. McReynolds' paper and thought his method was surely worth trying. The main point is that he uses the reduced and stable medial cortex of the os calcis as a fulcrum against or around which he molds the rest of the fracture fragments into proper place. Is that the concept you got out of it?

Dr. Henderson:

Yes, that is the understanding I got. The roentgenograms he presented at the meeting in Memphis showed excellent reductions and were quite impressive.

Edward D. Henderson, M.D.‡
Ray E. Santos, M.D.‡
Richard T. Chiroff, M.D.‡
Einer W. Johnson, Jr., M.D.‡
Rochester, Minnesota

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*Professor of Orthopedic Surgery, Mayo Graduate School of Medicine (University of Minnesota), Rochester and Consultant, Section of Orthopedic Surgery, Mayo Clinic, Rochester.

†Associate Professor of Clinical Orthopedic Surgery, Mayo Graduate School of Medicine, (University of Minnesota), Rochester, and Consultant, Section of Orthopedic Surgery, Mayo Clinic, Rochester, Minnesota.

‡From the Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

Robert L. Feldmann, M.D.

This cover was reproduced from a painting by Dr. Robert L. Feldmann, which received a Blue Ribbon at the AMA Art Exhibit in San Francisco in June, 1968.

"Eastern Shore" had its genesis during a trip taken by Dr. Feldmann and his youngest daughter. They had traveled from York across the Bay Bridge to Cambridge, Maryland, in search of sea gulls for purposes of painting. On the eastern shore by Hoople's Island, they found a crab factory and a number of desirable scenes. The painting from which the cover picture was taken was inspired here.

Dr. Feldmann's formal training in art was in charcoal during his junior and senior years of college. He belongs to a group of doctors in York who are cultivating their talents in painting. Water color remains his medium of choice.

He is a fellow in the American and Pennsylvania Academies of Ophthalmology and Otolaryngology and practices otolaryngology in York, Pennsylvania.

Meetings and Announcements

It is the province of knowledge to speak, and
it is the privilege of wisdom to listen.
O. W. Holmes

JUNE

Scott-Carver County Medical Society
  Annual Meeting, New Prague Country Club, 6:30 P.M., Tentative—June 3.

Freeborn County Medical Society
  Dinner Meeting—7 P.M., June 19, Location to be announced.

Waseca County Medical Society
  Regular Meeting, Waseca Memorial Hospital, 6:30 P.M., June 30.

American College of Cardiology and the Minnesota Heart Association.
  Seminar, June 30-July 3, Madden Inn, Gull Lake, Brainerd. Subject: Clinical Application of Cardiac Catheterization Data. Contact: William D. Nelligan, American College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

The Emergency Physician

The increasing patient loads in emergency departments across the country has underscored the need for a new type of physician—a specialist in emergencies: The Emergency Physician.

To assist this new breed of physicians the American College of Emergency Physicians was organized in August, 1968.

A nucleus of physicians—both from full-time and part-time emergency care groups in Michigan—chartered the American College of Emergency Physicians and have organized the College on a nationwide basis.

One of the main purposes of the College is to improve emergency services rendered to the patient. Other aims of the College are: to encourage and implement the training and continuing education of emergency physicians; to promote policy which preserves the integrity of private practice; to promote coordination of community emergency care facilities and personnel; to advance the ethical standards of the private practice of Emergency Medicine and Surgery.

For information write: Executive Secretary, American College of Emergency Physicians, 120 West Saginaw Street, East Lansing, 48823; or the representative in your area—Robert Ersek, M.D., 8806 Minnetonka Blvd., St. Louis Park, Minnesota 55426.

Seminar: Simulation of Biological Systems

A one-week, intensive seminar in the simulation of biological systems will be given July 14-18 (inclusive) 1969 at the EAI Los Angeles Analysis and Computation Center. The seminar will emphasize the development of models suitable for use on modern analog/digital/hybrid computers, without stressing, unduly, the details of programming any given type. Computer demonstration of various models with "hands on" participation will be included.

The seminar will cover the cardiovascular system, artificial kidneys, fluid and electrolyte distribution, hormonal control systems and neuronal and neuromuscular systems. The lecturers will include members of the Faculty, University of Southern California and the RAND Corporation. The fee of $280 will include all required notes and textual material.

For further information contact: Manager of Education and Training, Electronic Associates, Inc., Los Angeles Computation Center, 1500 E. Imperial, El Segundo, California 90245.

Otolaryngology Clinics

STARTING WITH this issue of MINNESOTA MEDICINE the Department of Otolaryngology of the University of Minnesota Medical School and Hospitals will sponsor an on-going series of brief and practical articles designed primarily to be of interest to the family physician. These Otolaryngology Clinics will be written by members of the departmental faculty with an occasional invited contributor.

Judging from two previous surveys conducted in the states of Minnesota and Iowa, the family physician spends an average of twenty per cent of his time dealing with disorders as they affect the ear, nose, throat, maxillofacial area and adjacent regions of the head and neck. This can range anywhere from a red-hot acute otitis media to laryngeal cancer.

An attempt shall be made to keep these articles brief and informal. Suggestions from the Profession for future topics will be greatly appreciated.

Michael M. Paparella, M.D.*
Minneapolis, Minnesota

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*Professor and Head, Department of Otolaryngology, University of Minnesota Hospitals.

The Nature of Otolaryngology

THIRTY YEARS AGO, the training in otolaryngology required for eligibility for Board certification was an 18-month period of residency training in an approved hospital or several years of apprenticeship.

The specialty of otolaryngology deals with the upper respiratory tract and its adnexa. This area includes the nasal spaces and maxillae, the ear connected through the eustachian tube, and the entire throat. The latter includes the structures in the nasopharynx, the oropharynx (which includes the oral cavity, the tonsils, and the soft palate) and the laryngopharynx, of which the larynx and the esophageal introitus are the principal areas.

Even though separate areas are involved which suggest special titles such as otology, rhinology and laryngology, the term otolaryngology is appropriate as a simplified title in that all three areas are connected by the upper respiratory tract and often share in the morbidity associated with infections anywhere in this tract. Some now prefer the term "otorhinolaryngology" to include the field of rhinology.

Broncho-esophagology became part of otolaryngology because of technical difficulties encountered in an adequate visualization of the bronchi and esophagus.

Prior to the advent of the antimicrobials, the major activity of otolaryngologists was concerned with suppuration and its complications in the upper respiratory tract.

Obviously, much less time is needed today to combat infection, and many of the old complications of upper respiratory suppuration are now relative rarities. Research and technical advances by otolaryngologists have been as dramatic as any specialty and have had a strong impact on progress.

In otology the use of the operating microscope has brought new gains in stapes surgery for otosclerosis and in reconstructive middle ear surgery after damage by chronic suppuration. The evaluation of hearing loss and an appreciation of the systemic and neurologic disorders has contributed to the advances in the field of otology.

In the field of rhinology functional disorders and allergic problems are more commonly diagnosed, better understood and managed now than prior to the antimicrobial era.

Reconstructive surgery of the nasal pyramid caused by injury or by improper development is now performed for chronic obstruction as well as for external deformity. It is a natural counterpart of the maxillofacial surgery for oncologic and traumatic disorders that constitutes an important field in otolaryngology.

In laryngology and bronchoesophagology practically the only disorder of the larynx that has decreased in incidence and severity is obstructive laryngitis caused by inflammatory swelling of the glottis. Antimicrobials, steroids and the management of these cases in an atmosphere of high humidity and controlled temperature have lessened the morbidity and the mortality.

The relative frequency of tracheostomy has increased. It is often performed early and electively in the better management of the hypoxic states that result from the accumulation of secretions in the trachea and bronchi.

Today minimum approved residency training in otolaryngology covers a period of four or five years.

There is abundant evidence that otolaryngology is organized to continue the remarkably accelerated progress of the past two decades. Its special societies are dedicated to research and education.*

Lawrence R. Boies, M.D.†
Minneapolis, Minnesota

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*American Otological Society, American Laryngological Association, American Triological Society, American Broncho-Esophagological Association, The Section on Otolaryngology of the American Academy of Ophthalmology and Otolaryngology, American Rhinologic Society, American Otorhinologic Society for Plastic Surgery, American Society for Facial Plastic Surgery, etc.

†Professor and Head Emeritus, Department of Otolaryngology, University of Minnesota Medical School. Director of Medical Affairs, Deafness Research Foundation.

Progress

Progress: When you're just getting used to something and somebody invents something better that you won't have time to get used to before somebody invents something better.—Howard Blake

Man is born with his hands clenched, but his hands are open in death, because on entering the world he desires to grasp everything, but on leaving, he takes nothing away.—The Talmud

Otalgia

Otalgia can be either primary or secondary. Primary otalgia refers to ear pain resulting from pathological conditions directly affecting the ear; secondary otalgia is that which is referred to the ear. Fifty per cent or more of all pain experienced in the ears of adults originates from another source. It is important to remember that otalgia may not be proportional in seriousness to the disease causing it.

Sensory Innervation of the Ear

Contributions from the Vth, VIIth, IXth and Xth cranial nerves and the cervical plexus provide afferent pathways for transmission of stimuli from the auricle, external auditory canal, middle ear, and immediately adjacent areas.

The auriclotemporal branch of the mandibular division of the Vth nerve supplies the skin of the tragus, the anterior and superior wall of the external auditory canal and sometimes the anterior limb of the helix and a portion of the crus. The auricular branch of the Xth nerve (Arnold's nerve) communicates with a branch of the IXth nerve and the VIIth nerve, and together these supply the concavity of the concha, posterior portion of the external auditory canal and corresponding segment of the external surface of the tympanic membrane, and a small area of skin on the posteromedial aspect of the auricle and adjacent mastoid region. The posterior branch of the great auricular nerve supplies the greater portion of the posterior surface of the auricle and the more posterior part of the lateral surface. There is overlap and communication with the lesser occipital nerve on the mastoid region. The innervation of the external surface of the tympanic membrane corresponds to that of the auditory canal. The tympanic branch of the IXth nerve supplies the inner aspect of the tympanic membrane.

The tympanic plexus constitutes the sensory innervation of the middle ear. The plexus is formed by the tympanic branch of the IXth nerve (Jacobson's nerve) and the superior and inferior cortico-tympanic branches of the sympathetic plexus of the internal carotid artery. One can therefore see, because of the complicated ramifications of the various nerves, that the cause of otalgia is often difficult to locate.

Etiology

Otalgia may have multiple causes (Table), and the diagnosis may be made only if a detailed examination is carried out.

External Ear and Canal

The cause of pain originating from the external ear and canal is easily recognized in most instances. An exception to this may be a very early neoplasm of the external canal. Examination of the external canal may be normal grossly, but if careful palpation of the quadrants of both the bony and the cartilaginous canal is carried out under adequate visualization using a tightly wound cotton-tipped wire applicator, the pain may be elicited.[1] Biopsy of the areas of pain should not be delayed because of the possibility of an early

TABLE

Causes of Ear Pain

Primary (Ear)

A. External Ear
   1. Furunculosis
   2. Foreign body in the external ear canal
   3. External otitis
   4. Abscess of auricle
   5. Perichondritis of auricle
   6. Eczema of the meatus
   7. Impacted cerumen
   8. Frostbite of auricle
   9. Herpes simplex and herpes zoster oticus
   10. Malignant and benign growth of external ear
   11. Fungal infections (otomycosis)
   12. Acute myringitis and myringitis bullosa
   13. Trauma of tympanic membrane and external canal

B. Middle Ear or Mastoid
   1. Acute otitis media
   2. Acute mastoiditis
   3. Acute aero-otitis media (barotrauma)

B. Middle Ear (continued)
   4. Acute eustachian tube obstruction
   5. Complications of otitis media and mastoiditis
      a. petrositis
      b. facial paralysis
      c. labyrinthitis
      d. inner ear deafness
      e. subperiosteal abscess
      f. extradural abscess
      g. subdural abscess
      h. brain abscess
      i. venous sinus thrombophlebitis
      j. meningitis
   6. Malignant and benign growth of middle ear and mastoid process

C. Idiopathic (tic-like pain confined to the ear)
   1. Geniculate complex of the VIIth nerve
   2. Tympanic branch of the IXth nerve

Secondary (Referred)

A. Larynx
   1. Cancer
   2. Ulceration
   3. Perichondritis and chondritis
   4. Arthritis of circoarytenoid joint

B. Pharynx (naso-, oro-, and hypopharynx)
   1. Pharyngitis
   2. Acute tonsillitis (palatine, lingual, pharyngeal)
   3. Peritonsillar abscess
   4. Retropharyngeal abscess
   5. Ulceration
   6. Post adenoidectomy or tonsillectomy
   7. Nasopharyngeal fibroma
   8. Malignant growth

C. Oral Cavity
   1. Dental neuralgias
      a. dentine exposed, pulp inflamed, or nerves dying
      b. unerupted and/or impacted wisdom or molar teeth
      c. traumatic occlusion of teeth, faulty jaw closure and improper denture fit
   2. Acute diffuse glossitis or stomatitis
   3. Carcinoma of tongue

D. Esophagus
   1. Foreign body
   2. Hiatus hernia
   3. Inflammation
   4. Malignant and benign growths

E. Miscellaneous
   1. Mumps
   2. Acute thyroiditis
   3. Trigeminal neuralgia
   4. Sinuses
      a. inflammation
      b. malignant and benign growth
   5. Temporomandibular arthritis
   6. Erysipelas

E. Miscellaneous (continued)
   7. Raynaud's disease
   8. Chilblains
   9. Postauricular lymphodenitis
   10. Glossopharyngeal neuralgia
   11. Sphenopalatine ganglion cephalgia
   12. Elongation of the styloid process
   13. Involvement of upper three cervical nerves
      a. whiplash injury and other cervical spine lesions
      b. inflammation such as tabes dorsalis or herpes
   14. Angina pectoris
   15. Thoracic aneurysm
   16. Innominate artery aneurysm
   17. Affections of nasal passageway
   18. Affections of lung and bronchus

malignancy. Middle ear affections should be recognized in most instances. Chronic infection of the middle ear does not usually cause ear pain. If pain occurs with chronic otitis media or chronic mastoiditis, an impending or existing complication is present.

Seventh and Ninth Nerve

Tic-like pain confined to the ear is a rare condition which may originate in either the geniculate complex of the VIIth nerve or the tympanic branch of the IXth nerve.[2] Definite diagnosis rests basically on the results of stimulation and section of the nervus intermedius and glossopharyngeal nerves within the cranial cavity, or similar maneuvers applied peripherally to the chorda tympani and Jacobson's nerve in the middle ear.

Tenth Nerve

Referred otalgia, through the superior laryngeal nerve of the vagus, may originate from lesions in the larynx and hypopharynx. Lesions in the area of the palatine, pharyngeal, and lingual tonsils and adjacent tongue may cause ear pain via the glossopharyngeal nerve. A branch of the trigeminal nerve will cause referred ear pain from dental and oral disease.

The manner in which the mandible is attached to the skull provides obvious chances for the condyle to impinge on sensory nerve branches (chorda tympani, auricular branches of the auriculotemporal nerve). Joint destruction does not have to be present to produce reflex pain. In the majority of cases, roentgenograms are normal.

Visceral Organs

Otalgia may be referred from visceral organs to the ear,[3] including the lung and bronchus by way of the bronchial branch of the vagus, esophogeal hiatus hernia, angina pectoris, and aneurysms of the innominate artery or thoracic aorta. Cervical spine lesions may cause referred otalgia from branches of the cervical plexus, principally the second and third cranial nerves.

Summary

1. Pain that is felt in the ear may not originate from the ear.
2. Ear pain of a referred nature requires intensive investigation of the larynx, pharynx, oral cavity, temporomandibular joint, sinuses, esophagus, lung cervical plexus and thoracic vasculature. In other words, any structure in the proximity of the nerves supplying the ear (cranial nerves V, IX, X, Cl-3, and sympathetics and parasympathetics) can refer pain to the ear.
3. Otalgia may not be proportional in seriousness to the disease causing it. A laryngeal carcinoma may cause only vague pain; whereas dental caries may cause severe pain.

Case Reports

The following four patients presented initially to the physician's office with a chief complaint of pain in the ear (otalgia). Two patients proved to have otalgia due to primary disease in the ear, while the other two demonstrated secondary or referred pain to the ear. Another common example of secondary or referred otalgia would be temporomandibular joint dysfunction.

Primary Ear Pain

Case 1

A female patient in her early 50's presented with excruciating right ear pain as her primary symptom. In the past she had received treatment for external otitis from other physicians. Routine otoscopy did not reveal a lesion but, with magnification, a small (3-4mm) irregular growth was noted on the lateral portion of the anterior bony canal wall. The trigeminal neuralgia-like pain was elicited by pinpoint palpation with a cotton-tipped wire applicator. An excision biopsy was performed and a diagnosis of squamous-cell carcinoma made.

Surgical treatment was instituted in July, 1963. This included block excision of the anterior half of the tympanic membrane, the entire anterior canal wall up to the tragus, the superficial lobe of the parotid gland, and the condyle of the mandible. The posterior bony wall was widened maximally with a drill, but a mastoidectomy was not performed. To date, there has been no recurrence of the growth and no further pain.

Case 2

This 37-year-old white female had experienced severe pain in her left ear for the preceding two and one-half years which was refractory to medical treatment. Approximately one year before this admission she had an excision of a small lesion from the left external canal by another physician. This was reported to be a cylindroma. However, postoperatively the pain persisted.

Examination of the left external canal showed it to be clear. The tympanic membrane was intact with normal landmarks. By careful otoscopy, a reddened elevated area in the posterior superior portion of the canal could be seen but no lesion could be identified. The area was very tender to touch as opposed to other parts of the canal. This was thought to be the area from which the previous tumor had been excised.

It was felt that it would be justified to consider a wide excision of this area with perhaps removal of cartilage and bone for exploratory purposes. In September, 1965, by means of a postauricular incision, the entire posterior and superior canal skin was extirpated and the bony canal was drilled down to achieve maximum exposure. A wide margin was excised around the lesion in piecemeal fashion. The pathology report indicated a ceruminoma. The patient has been doing well with no recurrence.

Secondary Ear Pain

Case 3

A male patient in his 50's was found to have squamous-cell carcinoma of the cervical esophagus in December, 1967. The lesion was treated with cobalt^{60}. He did well until January, 1969, at which time he started having dysphagia. Esophogram and esophogoscopy revealed a recurrence of his tumor. A second course of cobalt^{60} was started. After two weeks of therapy, the patient experienced severe left ear pain which awakened him at night and required analgesics for relief.

Examination of the left ear canal and tympanic membrane was normal. The left posterior external ear canal was very tender to palpation with a cotton-tip applicator. The rest of the canal, as well as the right external canal, was non-tender to palpation. Injection of the left external canal with 1% xylocaine with epinephrine, 1:1000, completely relieved the pain. Referred pain along the Xth cranial nerve took place here.

Case 4

A fifteen-year-old girl had a left upper molar extracted two days prior to being seen. She also had an impacted and infected lower molar on the left which was being treated with antibiotics before extraction. The main complaint of the patient was left ear pain. Examination of the external canal and tympanic membrane revealed no pathology. The posterior canal wall was tender to palpation. Injection of the external canal with 1% xylocaine and epinephrine, 1:1000, relieved the pain. Here referred or secondary ear pain occurred along the Vth cranial nerve.

C. Randall Nelms, Jr., M.D.*
Michael M. Paparella, M.D.*
Minneapolis, Minnesota

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*Department of Otolaryngology, University of Minnesota Hospitals.

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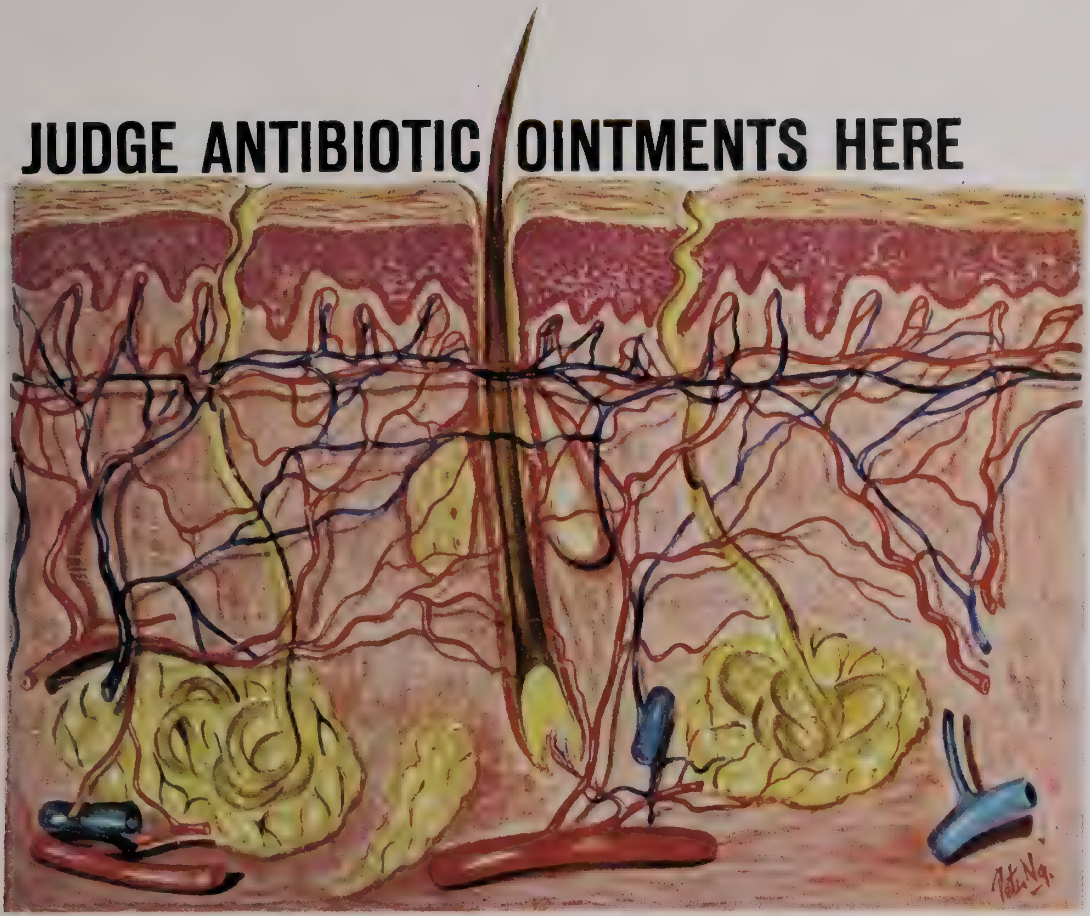

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Clinical Path Conference

Pulmonary Opportunistic Infections after Renal Transplantation

Dr. Thomas Mulrooney:*

A 48-year-old white female was admitted to Hennepin County General Hospital to receive a renal transplant. Chronic renal failure had been present for two years following chronic pyelonephritis. During that two-year period, the patient had been supported by chronic hemodialysis. Two months earlier she had undergone bilateral nephrectomy to assist in the control of hypertension and to prepare her for the transplantation.

The patient was a thin, alert, chronically ill-appearing woman in no acute distress. Her blood pressure was 150/100, her pulse 80 per minute, and her temperature 98°. Mild arteriosclerosis was observed in the optic fundi. The heart was not enlarged, but a loud, harsh, systolic murmur was audible over most of the precordium and was transmitted into the neck. The lungs were clear. Apart from old surgical scars of the abdomen, the remainder of the physical examination was normal.

Laboratory Studies

Laboratory studies included hemoglobin 9.8 grams %; white blood cell count 7800 per cu. mm. with 79% neutrophils, 19% lymphocytes and 2% eosinophils. Serum electrolytes revealed serum sodium 134 mEq/L; potassium 4.8 mEq/L; chloride 94 mEq/L and CO_2 21 mEq/L. Serum proteins, calcium, alkaline phosphatase, bilirubin and fasting blood glucose were all normal. The blood urea nitrogen was 70 mg. %. An EKG showed a first degree A-V block and increased voltage in the left precordial leads thought compatible with left ventricular hypertrophy. A chest roentgenogram was normal.

Hospital Course

On the third hospital day, the patient received the left kidney of a cadaver donor which was ingrafted into the patient's right flank. The surgical procedure was well tolerated and Azathioprine and prednisone were given to prevent rejection.

On the tenth day following surgery the patient experienced a rise in temperature to 103° and developed a non-productive cough. Scattered wheezes and rhonchi were audible in both lung fields. The white blood cell count was 8400 per cu. mm. with 90% neutrophils, 7% lymphocytes and 3% monocytes. The BUN was 132 mg. % and the serum creatinine 2.1 mg. %. Serum electrolyte determinations were again normal. A chest roentgenogram showed bilateral pulmonary infiltrations, particularly involving the hilar areas of the lung. The venous pressure was 15 cm. of water and a circulation time with decholin was 15 seconds. Her intake of sodium in water was restricted and she was treated with furosemide and cephaloridine. Sputum smears revealed a mixture of Klebsiella species and Candida albicans. She continued to receive prednisone 40 mg. daily and Azathioprine 50 to 100 mg. daily.

Over the next several days her condition deteriorated and roentgenograms demonstrated progression of the pulmonary infiltrations. On the 16th day after transplantation an open lung biopsy was performed and Azathioprine was discontinued. Touch imprints of the lung biopsy specimen were stained with Geimsa stain, and organisms suggestive of pneumocystis carnii were felt to be present. The pathologic diagnosis for the lung biopsy was interstitial pneumonitis, and special stains for bacteria, fungi, acid-fast bacilli and pneumocystis carnii were negative. Repeated examinations of sputum for these organisms were also negative and cultures grew Klebsiella and occasional colonies of Candida albicans.

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*Staff, Department of Internal Medicine, Hennepin County General Hospital.

Following the lung biopsy, the patient was given pentamadine isethionate 225 mg. daily as well as cephalothin and methyl prednisolone. Because of deterioration of renal function and suspected rejection, she received a course of radiotherapy to the transplant site and her corticosteroid dose was increased to 100 mg. of methylprednisolone daily. With this treatment program she became afebrile although her white blood cell count remained near 15,000 per cu. mm. with about 99% neutrophils. She became less dyspneic, and gradual clearing of the pulmonary infiltrates was observed on chest roentgenograms. However, her renal function became progressively impaired and hemodialysis was necessary. It was decided that her transplanted kidney had been conclusively rejected, and 12 days after her lung biopsy the renal transplant was removed.

The patient did well for three days and then abruptly developed increasing dyspnea. Rales were audible over both lung fields. Her chest films showed progression of the diffuse pulmonary infiltrations. During the next several days her air hunger became steadily worse and no improvement was observed despite increases of corticosteroids and administration of chloramphenicol, colistin, and gamma globulin. She became severely hypoxic, requiring tracheostomy and assisted ventilation with a mechanical respirator. Despite the administration of 100% oxygen, her arterial tensions were never in excess of 50 mm. of mercury. On the ninth day following removal of the transplanted kidney, the arterial oxygen tension was 48 mm. of mercury, CO_2 tension 32 mm. of mercury, and pH 7.53. At this time, the hemoglobin was 11.9 grams % and the white blood cell count 5600 per cu. mm. with 96% neutrophils and 4% lymphocytes. Serum electrolytes were normal except for a CO_2 of 32 mEq/L. The BUN was 69 mg.% and the creatinine 3.9 mg. %. Thereafter, the patient became increasingly unresponsive and two days later she expired. Death occurred 37 days after the renal transplantation and 11 days after removal of the rejected kidney.

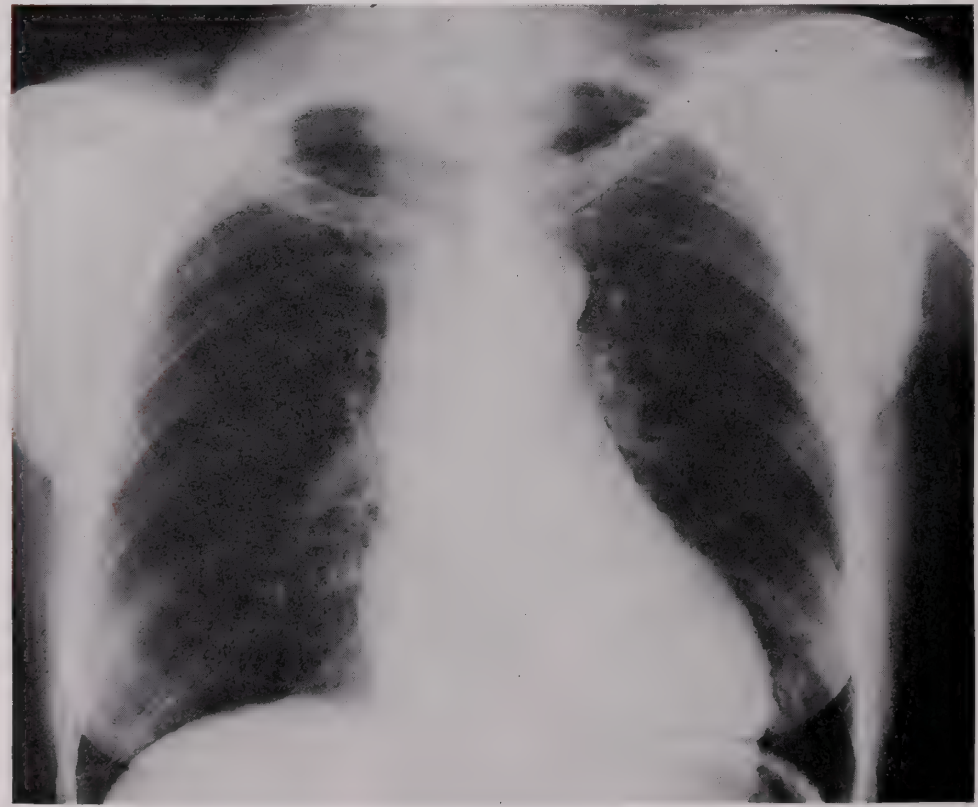

Fig. 1—Chest roentgenogram showing slight pleural effusions without pulmonary infiltration.

Clinical Discussion

Dr. James Lillehei:*

The problem presented by this case is essentially that of a 48-year-old white female who was admitted to the hospital to receive a renal transplant after two years of chronic hemodialysis. Two months before this hospitalization she had had a bilateral nephrectomy to assist in the control of hypertension. Significant physical findings included a slight elevation of blood pressure and a systolic heart murmur. The lungs were clear at that time.

The laboratory studies revealed an anemia with a normal differential count. Blood chemistries were normal with the exception of a BUN of 70 mg.%. She had an electrocardiogram abnormality, namely a first degree A-V block and findings that were suggestive of left ventricular hypertrophy. Her chest roentgenogram was normal.

On the third hospital day she underwent renal transplantation with a cadaver kidney and the surgical procedure was well tolerated. On the tenth day following surgery her course became complicated by fever and a non-productive cough. The white blood cell count remained essentially normal except for a more prominent shift to the left. Her BUN was markedly elevated to 132 mg.%. Then for the first time, about 10 days after the procedure, the chest roentgenogram showed bilateral pulmonary infiltrations. I assume that congestive heart failure was considered at that time since a venous pressure and circulation time were found to be normal. I wonder if this might not be an appropriate time to have the x-ray studies?

Radiological Findings

Dr. Mario Pleigo:†

A large number of x-ray studies were done on this patient. All chest

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*Associate Professor of Medicine, Chief of Section of Pulmonary Disease, University of Minnesota Hospital.

†Associate Radiologist, Hennepin County General Hospital.

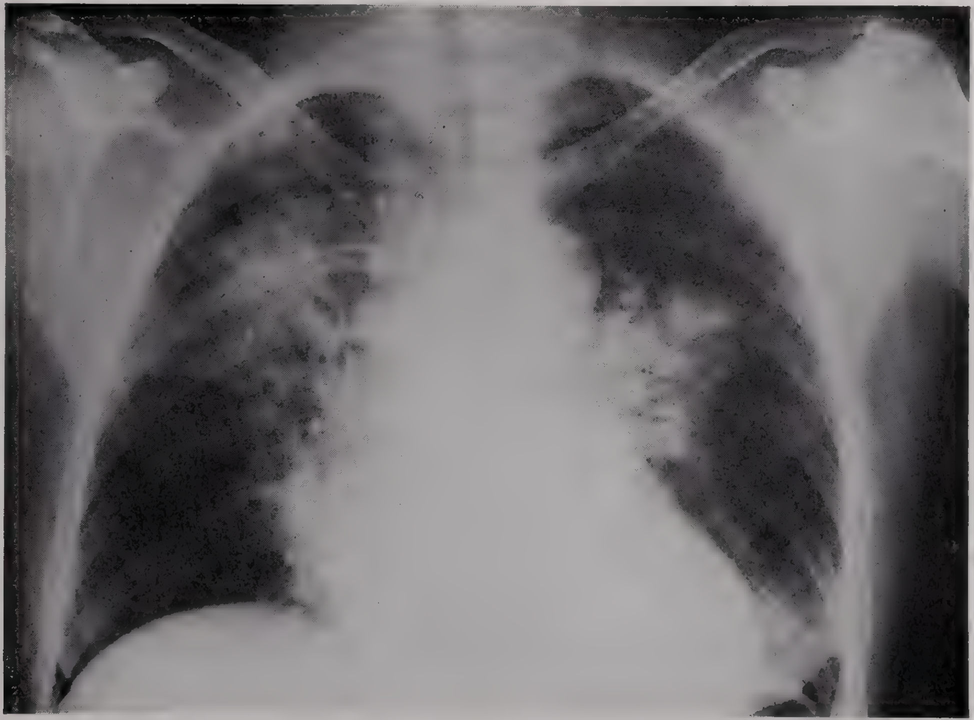

Fig. 2—Chest roentgenogram with bilateral alveolar infiltrations fanning out from the hilar areas to the upper lobes.

roentgenograms show cardiac enlargement with left ventricular predominance and what was interpreted as central pulmonary congestion. On a film in early December (Figure 1) bilateral slight pleural effusions were noted, and then on the film dated December 15 (Figure 2) we began seeing nodular mottled densities in both hilar areas. It is difficult to differentiate these findings from pulmonary edema or uremic pneumonitis, and I am sure those diagnoses were considered. We could not give a definite suggestion of an etiologic agent for the bronchopneumonia from the appearance of the chest x-ray, although lung transplant syndrome was considered.

Hereafter, the radiologist must evaluate the changes on serial roentgenograms and the process appears to evolve into an infiltrative pneumonia with upper lobe involvement that we could not distinguish from acute pulmonary tuberculosis. As the x-ray findings evolve they appear to show a perivascular pattern with an alveolar infiltration, particularly in the upper lobes. Some component of uremic pneumonitis could be present as well.

Dr. Lillehei:

The x-ray findings appear non-specific; however, sputum cultures revealed Klebsiella Enterobacter species sensitive to an antibiotic being used. She continued to receive prednisone in moderate dosage and Azathioprine in 50-100 mg. daily dosage. Over the next several days a progression of the pulmonary infiltrations occurred, and on the 16th day after transplantation, the patient had an open lung biopsy and treatment with Azathioprine was discontinued. The biopsy specimen revealed an organizing interstitial pneumonitis, thickening and fibrosis of the interalveolar septa, and a predominantly mononuclear cell infiltrate. Cultures of the biopsy specimen showed only Candida albicans. Special histochemical techniques failed to reveal an infecting organism. However, following the biopsy the patient was treated with pentamadine isethionate since pneumocystis carnii cysts were suspected on a Geimsa stain. It is very important in this setting to have imprint touch preparations from the surface of the lung biopsy specimen, since this diagnosis can sometimes be made. The main advantage of this technique is that the specimen can be stained and examined immediately and assist the physician with therapeutic efforts. With some opportunistic pathogens, particularly pneumocystis carnii, one or two days could make a difference between the patient living or dying. There is good reason to emphasize doing lung imprints as was done here.

In the meantime, the patient was felt to be rejecting her cadaver transplant kidney. A course of radiotherapy was given to the transplant site and the steroid dosage was increased. With this treatment program she became afebrile and less dyspneic, with some improvement in the pulmonary infiltrations. Of course it was not clear which of the medications she was being given was accounting for the improvement of the x-ray picture. By 12 days after lung biopsy, renal rejection was felt to be definitely established and the cadaver transplant was removed. She did well for a few days and then became increasingly dyspneic. Pulmonary findings increased and the infiltrative process in the lung became more generalized. Thereafter, her course was relentlessly downhill in spite of drugs and mechanical ventilation.

Uremic Pneumonitis

Uremic pneumonitis has been mentioned for several years as producing this type of picture. However, we have great difficulty in separating uremic pneumonitis from pulmonary edema, and now it is becoming increasingly difficult to distinguish this form of pneumonitis from the opportunistic pneumonias. Notice that the patient's BUN was modestly elevated at 69 mg.%; so it is difficult to attribute the progression of the pulmonary infiltration to uremic pneumonitis.

Lung Transplant Syndrome

Lung transplant syndrome is a term which has been applied to this type of clinical situation, and the criteria for the diagnosis include an x-ray picture of lung infiltration associated with renal rejection and pathology which is immunologically non-specific. This syndrome frequently responds to steroid therapy. It is felt that transplantation lung is some sort of immunologic phenomenon based on the similarity of antigens from the lung basement membrane and renal tissue. Therefore, when the kidney is being rejected, the lung takes part in the immunologic insult. The non-specific findings on lung biopsy would be compatible with the diagnosis of transplantation lung. The argument that this is an immunologic phenomenon rather than an opportunistic infection is based on the response to high dose steroids. In this case, I would discard this diagnosis because a response to steroids does not necessarily mean that an immunologic phenomenon is occurring.

We now know from our early experience with opportunistic infections that the use of steroids may make the infiltration disappear and the patient may be made afebrile and gain a sense of well-being. We have had one patient with pneumocystis carnii pneumonia who had a very dense pulmonary infiltrate that responded to increased steroid dosage by completely disappearing within one month. Therefore, the disappearance of the infiltration with steroids should not be used to indicate that the disease process was an immunologic phenomenon. I do not know whether there is such a thing as transplantation lung; I would keep my mind open at this point. At the present time, I think that most of these pulmonary infiltrations are related to infections with specific organisms rather than an immunologic phenomenon.

Opportunistic Infections

The pattern in this patient is becoming increasingly familiar in certain hospitals in which transplantation programs are in progress. In these centers. immunosuppressive drugs are being given for treatment of a variety of conditions, including leukemias, lymphomas, and occasionally carcinomas.

At this point, I would like to put in a plea for the use of needle biopsy of the lung in this type of patient with a progressive lung problem. In the presence of these overwhelming opportunistic infections, a definite diagnosis must be made since the treatment for each condition is significantly different. The treatments for these opportunistic organisms are frequently quite toxic, and it is not going to be possible to put patients on a number of these toxic agents at any one time. I think we are going to have to make specific diagnoses and individualize therapy in each case.

In the Table, you will notice the autopsy findings in a series of 60 patients who died after renal transplantation at the University of Colorado Hospitals.[1] The authors thought that the organism listed at the left hand margin was the cause of death; the organism in the second column was found in association but felt to be incidental. In 15 of these patients, the infecting organism causing death was pseudomonas species. This bacterial infection caused death in a quarter of the patients since no adequate antibiotic agents to treat pseudomonas infections were available. The remainder of the pulmonary opportunists listed in the table can cause pulmonary infiltrations similar to those seen in our case. A number of pathogenic fungi, pneumocystis carinii, cytomegalic inclusion virus, and other bacterial organisms were frequently noted.

TABLE
Organisms Recovered at Autopsy (Sixty Patients)

	Cause of Death (no.)	Ancillary Infection (no.)
Pseudomonas	15	1
Paracolon, Klebsiella, Esch. coli	7	2
Staphylococcus, Pneumococcus	3	
Nocardia	3	
Aspergillus	7	
Candida	9	6
Histoplasma	1	1
Pneumocystis	2	7
Hepatitis	1	
Cytomegalovirus		30
Herpes zoster		1
Herrellea		1
Serratia		1
M. tuberculosis		2
Sporozoon, unidentified		1
Totals	48	53

Pneumocystis Carinii

We have now had six patients with immunosuppressive drug therapy who were found to have pneumocystis carinii infection. The diagnosis was made on two occasions by finding the organism in the sputum after staining with methenamine silver technique. When we cannot make a diagnosis by examination of the sputum, and the patient is extremely ill, we do a needle biopsy; and we have obtained a positive diagnosis in four instances. One of our patients had an open biopsy and the other three a needle biopsy. We have not missed a case of pneumocystis carinii pneumonia with a needle biopsy as yet. Aspiration of the pulmonary infiltrate transthoracically with a #18 needle has been unsuccessful in demonstrating pneumocystis in our hands.

Cytomegalic Inclusion Disease

Cytomegalic inclusion virus and pneumocystosis probably occur in many normal individuals as a latent infection. Autopsy studies on patients dying of a variety of diseases reveal a frequent association of viral inclusion bodies and pneumocystis. Notice that 57% of the autopsy series from the University of Colorado had associated cytomegalic inclusion virus with or without other pathogenic agents.

I might also mention that serologic testing for cytomegalovirus is worthwhile in young individuals because their incidence of titres to cytomegalovirus is low. In adults, this is not of much help since it has been reported that up to 80% of the patients over 35 have positive titres to cytomegalic inclusion virus. Apparently most of us come in contact with cytomegalovirus during our early life and a positive serologic test is not diagnostic.

Although cytomegalic inclusion virus was not considered a cause of death in the patients in the University of Colorado series, I would consider this agent as possibly being lethal in this case. I would like to remind you that it is very difficult to decide exactly what infectious agent causes death. The reason for this is that almost all of the organisms which can act as pulmonary opportunists can be found in various clinical situations or in normal persons. The reason I feel that cytomegalovirus can cause pneumonia and death relates to some case reports in the literature plus at least one of our cases of proven pneumocystis carinii infection in a patient with leukemia. We found the pneumocystis and treated the patient for pneumocystosis; he did not respond and died. This represented our first failure treating pneumocystis after two good responses, and at autopsy cytomegalic inclusion virus was found in large numbers in the lungs in addition to some persisting pneumocystis. I am beginning to think that cytomegalovirus kills patients under these circumstances.

Dr. Robert L. Strom:*

Dr. Lillehei, although it is not mentioned in the protocol, it is notable that this patient developed a vesicular eruption on the right flank and also on the mucous membrane of the vulva which was felt to be consistent with varicella-zoster virus infection.

Dr. Lillehei:

That is a good point because this kind of patient again is very susceptible to herpes virus and varicella-zoster virus as the result of altered immunity. Other viral agents and pathogens may also be found. Mycoplasma pneumonii infections have been suspected but not verified in a small study in this patient population. Nevertheless, patients with mycoplasma pneumonii infection often have cold agglutinins demonstrable in their serum. It is of interest that nearly one third of the patients who died after transplantation at the University of Colorado showed the presence of cold agglutinins in their serum and yet mycoplasma pneumonii were not found.

In conclusion, I believe that the patient developed an opportunistic infection perhaps due to multiple organisms in association with immunosuppression. The x-ray picture and laboratory findings, although helpful, do not allow me to isolate a specific bacterial or fungal agent which might have caused death. I feel that it is highly likely that cytomegalic inclusion disease will be found in the autopsy.

Clinical Diagnosis: Status post rejection of cadaver homotransplant.
Fungal and bacterial infection of the lung after immunosuppression.
Cytomegalic inclusion disease of the lung.

Pathology

Dr. Strom:

The deliberate suppression of immunity in order to favor transplanted organ survival has now introduced a wide variety of remarkable infections, particularly pulmonary opportunistic infections. It is possible that these infections will become the limiting factors to the success of transplant procedures. An increase in prevalence of overwhelming pulmonary mycotic infection lays a burden on both the clinician and the diagnostic laboratory. Without discerning clinical judgment and awareness, the diagnosis of these infections may be made only by the pathologist at post-mortem examination.

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*Associate Pathologist, Hennepin County General Hospital.

On post-mortem examination, ruptured vesicles were noted over the right flank and vulva and these were found to be subepidermal vesicles characteristic of those caused by varicella-zoster virus. Some of the bullous lesions on the right flank were secondarily infected with the pseudomycelia of Candida species. The association of varicella-zoster virus skin vesicles localized to a skin dermatome which has been given therapeutic radiation in a patient undergoing immunosuppression has been well described.[2] Presumably this is due to activation of a latent virus infection in the dorsal root of the affected dermatome. Additional studies need to be done before the true nature of the pathologic process, which allows expression of latent virus infections, can be illucidated.

Each chest cavity contained approximately 500 cc. of serosanguineous fluid. The lungs were extremely heavy, with a combined weight of 2300 grams.

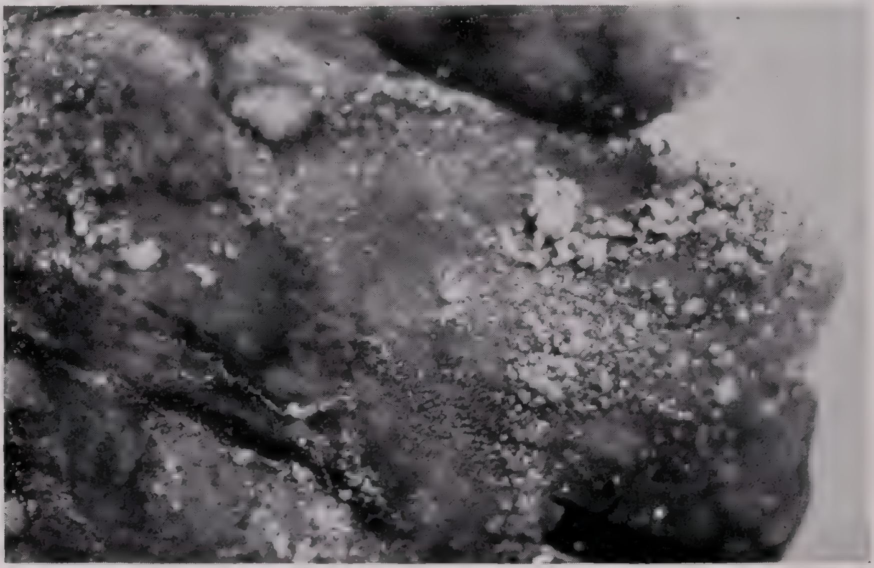
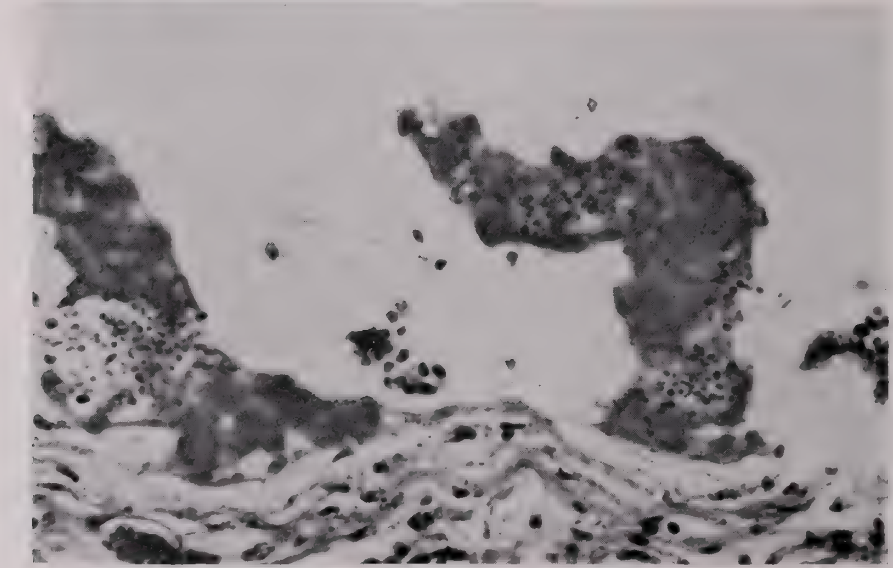


Fig. 3—Discrete granulations and encrustation of pleural surfaces due to Candida albicans.



Rig. 4—400X Gram-positive blastospores and pseudohyphae due to Candida albicans infections of the pleural surface.

The lung surfaces were indurated to palpation and many discrete rounded granulations were noted on the pleural surfaces (Figure 3). These unusual small, round granulations were unfamiliar to us and we did not appreciate their etiology until after microscopic examination of the tissue. In some areas, the pleural surfaces showed a light yellow encrustation, and we now know that this represents candidiasis of the pleural surface. Budding pseudohyphae and blastospores, which were gram-positive and compatible with Candida albicans infection, were present on the pleural surface (Figure 4).

I think one of the problems with needle biopsy is that we are biopsying at the periphery of the lung, while many of the opportunistic infections occur as central infarctions in the deep lung tissue. As seen on x-ray and in this cut surface of the lung at autopsy, much of the lesion is centrally placed (Figure 5). The zone of infarcted pulmonary tissue is seen centrally, and proliferating fungus with invasion of pulmonary veins and associated focal arterial thrombi are seen on histologic examination. On microscopic examination of the lung tissue, we see proliferating fungal hyphae standing out against a background of lung alveoli and the hyphae appear gram-negative. The angle of the branching of these septate mycelia is approximately 45°, and they are highly suggestive of mycelia of Aspergillus species (Figure 6). Budding pseudohyphae of Candida species are similarly occasionally observed in the lungs. In addition, cytomegalic inclusion virus was present in the lung sections with hemorrhage into the adjacent alveoli (Figure 7). Here we see ballooned-up alveolar lining cells with eosinophilic cytoplasm and a large red intranuclear inclusion surrounded by a halo with margination of the chromatin around the periphery of the nucleus. The red cytomegalic inclusion bodies in the nucleus are made up of DNA and virus material. Some of the cytomegalic inclusion cells we observe also contain basophilic inclusions in the cytoplasm. These are felt to be a combination of DNA and RNA.

The heart weighed 450 grams and a small mural thrombus was present at the apex of the left ventricle. Within the septum and in the left ventricular wall, we observed multiple small round areas of hemorrhagic necrosis with yellow centers and hemorrhagic margins. Microscopic sections taken through

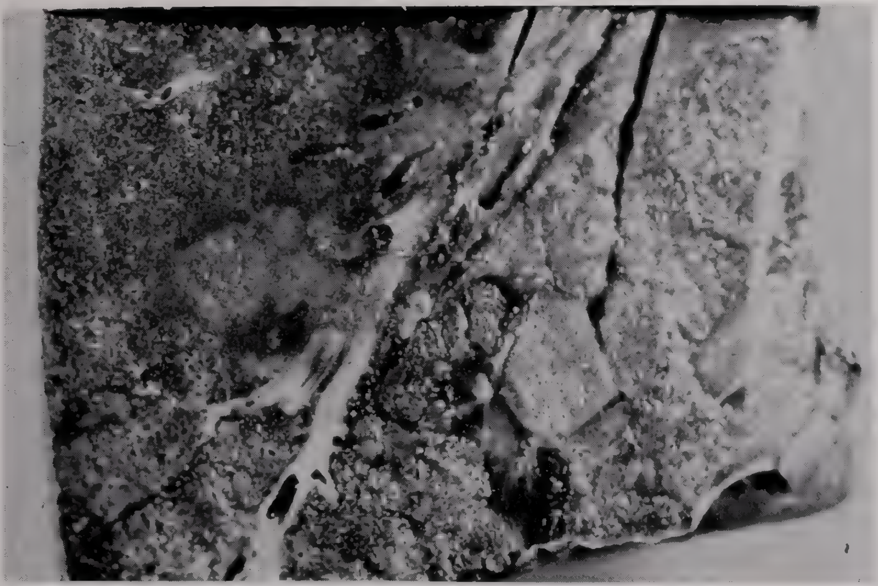


Fig. 5—Cut surface of lung with central zone of infarction due to fungal arteritis.

these areas revealed a fungal arteritis with branching septate hyphae suggesting infection with Aspergillus species. The thyroid gland was similarly infected with branching hyphae of Aspergillus species.

The liver revealed focal acute hepatic central congestion and atrophy without evidence of infection with salivary gland virus. The pancreatic substance similarly contained foci of necrosis, and examination of the acinar cells adjacent to the areas of necrosis failed to show evidence of cytomegalovirus. In other cases of our transplant series we have seen erosive processes and areas of necrosis in the pancreas, and I have ascribed this to the immunosuppressive therapy.

A few sharply punched-out, circumscribed ulcers were noted in the mucosa of the antrum of the stomach and considerable hemorrhage was present in the bowel lumen distal to the ligament of Treitz. A gram stain of the gastric

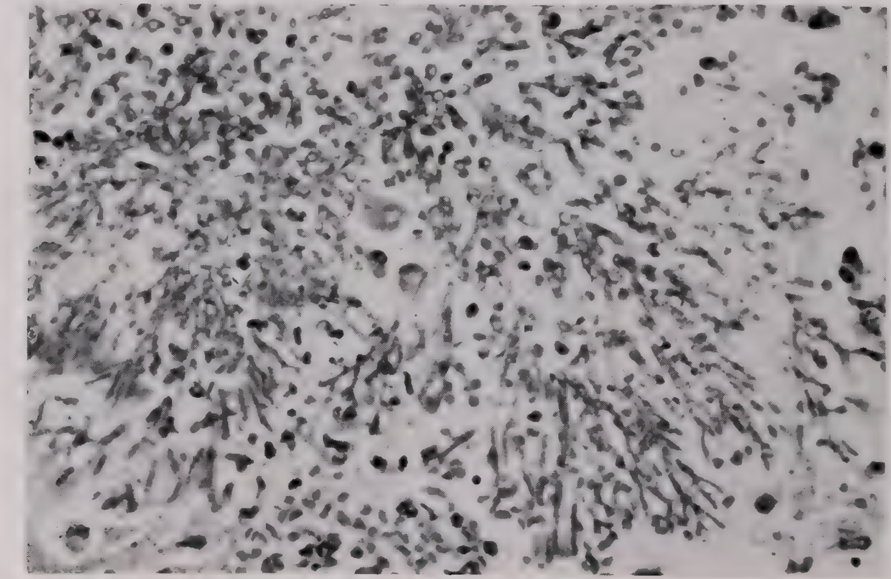


Fig. 6—400X Branching septate hyphae of Aspergillus fumigatus in section of lung tissue. Hematoxylin and Eosin.

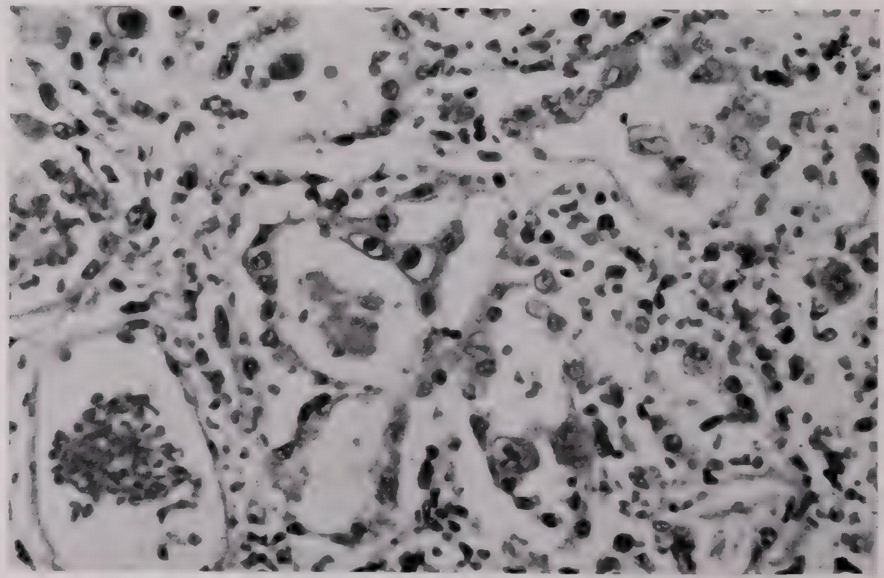


Fig. 7—400X Large red inclusion bodies of Cytomegalovirus in the nuclei of cells lining alveolar septae.

mucosa in these sites showed proliferating pseudomycelia of Candida albicans. In the series of patients with systemic candidiasis reported from the University of Colorado, the portal of entry of the Candida organisms was frequently the gastrointestinal tract.

The brain sections on this patient were very striking, showing multiple foci of hemorrhagic necrosis (Figure 8). Many of the zones of hemorrhage and necrosis occurred at the corticomedullary junction; these hemorrhages in regional infarcts are frequently present with an embolic infection of the central nervous system by Aspergillus fumigatus. Proliferating Aspergillus mycelia can be observed in vessels of the meninges confirming the presence of a mycotic meningitis. Some of the hemorrhagic zones in the brain abut on the leptomeninges, and up to 10 to 15% of a series of cases of Aspergillus infections of the central nervous system may be associated with fungal growth in the cerebrospinal fluid. On microscopic examination of the brain, one sees

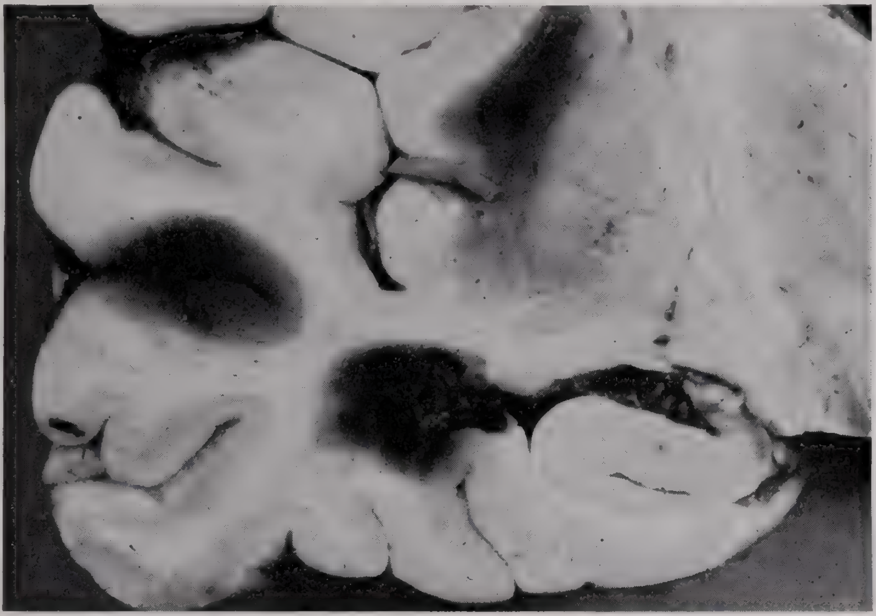


Fig. 8—Brain hemorrhages and infarction secondary to fungal arteritis caused by Aspergillus fumigatus.

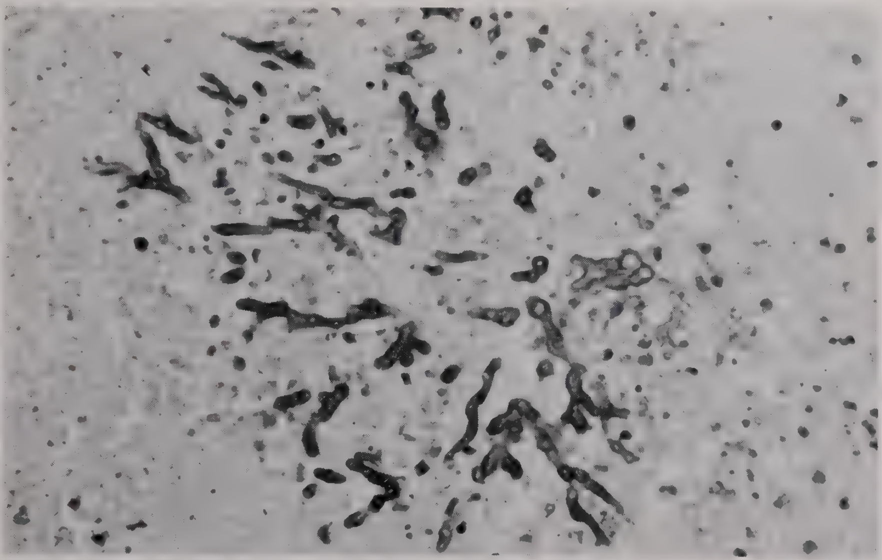


Fig. 9—400X Ray-like septate hyphae of Aspergillus fumigatus in brain tissue.

an active fungal arteritis with proliferating mycelia extending through the arterial walls and obstructing the lumen of vessels. Hemorrhagic infarctions are seen in the surrounding brain tissue and fungal mycelia in the brain substance itself. A PAS stain of the branching hyphae is confirmatory evidence that these are septate hyphae of Aspergillus species (Figure 9). On gram stains of the brain, one could see a mixture of gram-positive pseudomycelia and gram-negative branching true hyphae, suggesting that the nervous system was infected with both Candida and Aspergillus species.

Dr. George Kitzmiller:*

Do you need a special culture medium for isolation of Aspergillus species?

Dr. Strom:

No, that is not necessary; Aspergillus species grows extremely well on Sabouraud's agar or even human blood agar. Aspergillus species is a ubiquitous organism; it is carried by the ambient air in the bacteriology laboratory and may fall on our culture plates. The important thing to realize is that with this sort of problem you have to be suspicious of Aspergillus as a pathogen and ask for fungus cultures for Aspergillus on Sabouraud's medium. In this case, we did not grow the Aspergillus species from the lung or spinal fluid. In the University of Colorado series, they had difficulty isolating Aspergillus species from the sputum. Positive cultures of the fungal pathogen were isolated in only six out of 13 cases of fungus infection with pulmonary involvement.

University of Colorado Experience

I would like to comment further on the experience at the University of Colorado with opportunistic infections following renal transplantation.[3,4] Systemic fungus infection was found to be present in twenty-three of fifty-one patients who died following renal homotransplant for an incidence of 45%. The fungal agent causing the infection in twelve cases was Candida species, in five cases Aspergillus species, in two cases Nocardia species, in one case Histoplasma capsulatum, and in three instances combinations of the above infecting fungi. With regard to organ involvement by the systemic fungus infections, the pulmonary tract was involved in nineteen of the twenty-three patients who died of fungus infection. The gastrointestinal tract was involved in nine cases, the central nervous system in eight, the kidneys in four, and other organs in ten cases. The cases of Aspergillus infection showed a definite predilection for the central nervous system with five out of seven cases showing central nervous system involvement. Cases with systemic candidiasis showed a predilection for involvement of the gastrointestinal tract; in four of these cases, gastrointestinal tract involvement was present without lung involvement, suggesting an intestinal portal of entry.

Predisposing Factors

Those patients with systemic fungal infection after renal transplantation were slightly older than the average age group in the renal transplant deaths, and there was a striking male predominance, with twenty-two out of twenty-three cases of fungal infection occurring in males. The series with and without fungal infection showed no difference in dosage of immunosuppressive drugs or duration of antibiotic therapy. Sputum culture revealed the infecting fungus in six of fourteen patients for an incidence of 43%. Ante-mortem diagnosis and institution of treatment for systemic fungal infection occurred in only two patients. Concomitant bacterial, viral, or parasitic disease was present in 87% of patients. Included in this series were five cases of infection with pneumocystis carinii and thirteen instances of infection with cytomegalic inclusion virus. The incidence of cytomegalic inclusion virus infection in these patients was 57%: an extremely high incidence. There was an association between infections with pneumocystis carinii and high-dose steroid therapy. The majority of the cases of pneumocystosis were on high doses of steroids for over three months, whereas the systemic fungal infections occurred somewhat earlier. The systemic fungal infections developed on an average of sixty-seven days post transplantation; and after onset of clinical symptoms, the average time to death was 23 days.

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*Staff physician, Hennepin County General Hospital.

Most of the cases of systemic candidiasis in the literature are associated with long-term antibiotic therapy and the portal of entry is frequently an indwelling polyethylene catheter or the gastrointestinal tract. This has been recognized particularly in association with the tetracycline group of drugs.

One of the paradoxes in the data from the University of Colorado is that the incidence of infection does not correlate with the dosage level or duration of therapy with immunosuppressive agents and antibiotics. Systemic fungal infections are seen with steroid therapy alone, but the combination of steroid therapy and immunosuppression appears to heighten the susceptibility of the patient to disseminated fungus infection. Similarly in experimental animals, pretreatment with steroids and immunosuppressive agents leads to a high incidence of systemic fungus infection. If you give the animals just the fungal agent without the associated antibiotics and immunosuppressive drugs, experimental infection is frequently not produced.

In summary, our case represents an opportunistic infection with multiple organisms following renal transplantation. Candida albicans and Aspergillus fumigatus were felt to have disseminated widely from the lung and the gastrointestinal tract with dissemination to the brain. An associated cytomegalic inclusion virus infection of the lungs was present.

Final Anatomic Diagnosis:

1. Systemic aspergillosis and candidiasis involving the lung, gastrointestinal tract, heart, thyroid, and brain.
2. Cytomegalic inclusion virus infection of the lungs.
3. Varicella-zoster virus infection of the skin.
4. Status post rejection of cadaveric renal homotransplant.

Robert L. Strom, M.D.
Minneapolis, Minnesota

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The reason why some people have their backs against the wall is that they've been keeping up a front.—Inez Ozburn

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References: 1. Vernier, R. L., in Patient Care Feature: *Patient Care, 1*:20 (Feb.) 1967. **2.** Beeson, P. B.: "The Infectious Diseases," in Beeson, P. B., and McDermott, W. (eds.): *Cecil-Loeb Textbook of Medicine*, ed. 12, Philadelphia, W. B. Saunders Company, 1967, p. 230.

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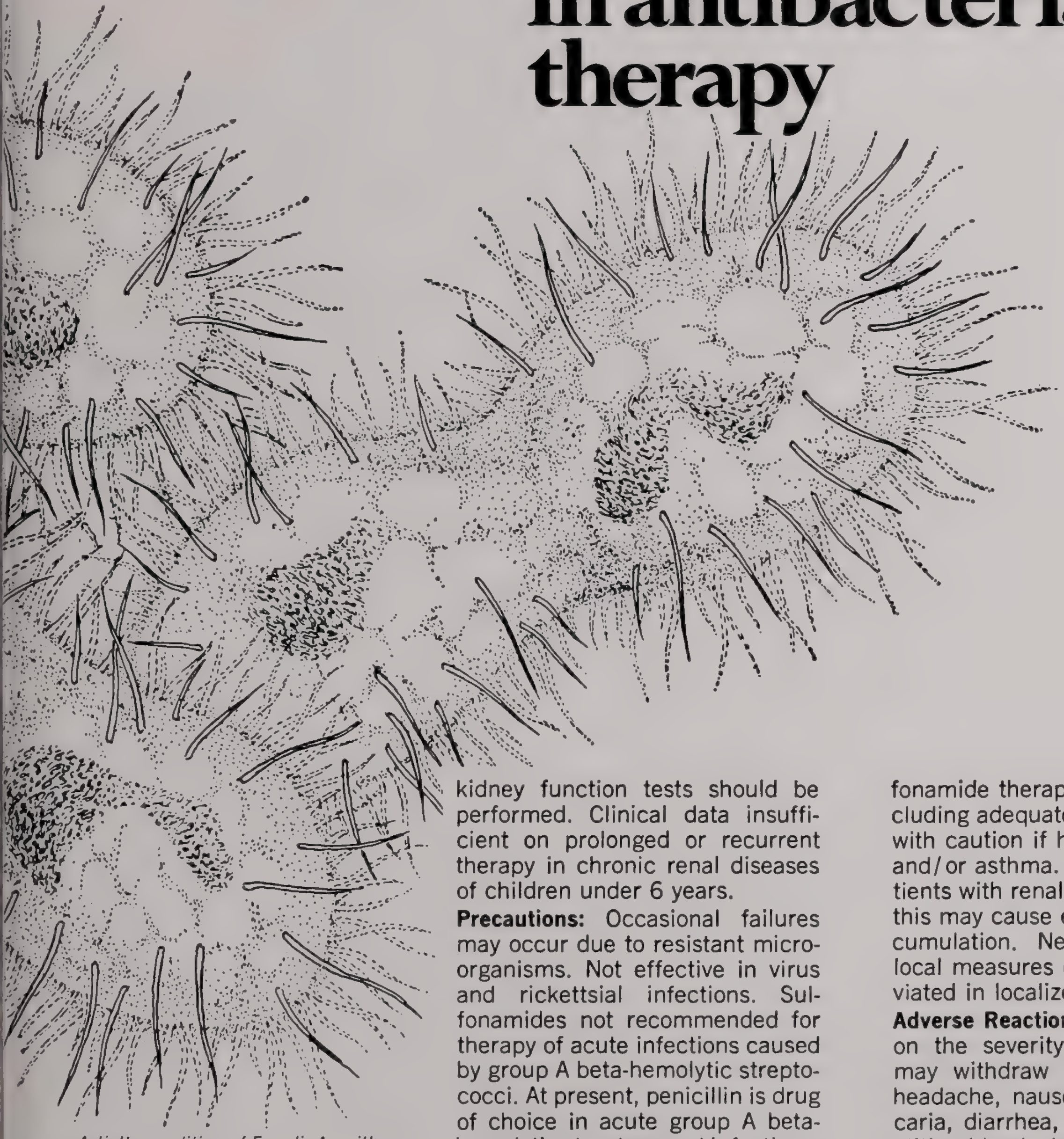

Artist's rendition of E. coli. As with most strains of E. coli, these have flagella and are motile.

kidney function tests should be performed. Clinical data insufficient on prolonged or recurrent therapy in chronic renal diseases of children under 6 years.

Precautions: Occasional failures may occur due to resistant microorganisms. Not effective in virus and rickettsial infections. Sulfonamides not recommended for therapy of acute infections caused by group A beta-hemolytic streptococci. At present, penicillin is drug of choice in acute group A beta-hemolytic streptococcal infections; although Gantanol has produced favorable bacteriologic conversion rates in this infection, data insufficient on long-term follow-up studies as to its effect on sequelae of rheumatic fever or acute glomerulonephritis. If other treatment cannot be used and Gantanol is employed in such infections, *important that therapy be continued in usual recommended dosage for at least 10 days*. Observe usual sulfonamide therapy precautions, including adequate fluid intake. Use with caution if history of allergies and/or asthma. Follow closely patients with renal impairment since this may cause excessive drug accumulation. Need for indicated local measures or surgery not obviated in localized infections.

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Continued to page 992

Advance

Candidiasis: Systemic and Disseminated

THE SIGNIFICANCE of isolating strains of *Candida* in a given case is often difficult to establish, because these organisms may be members of the normal body flora. Also *Candida* organisms may be isolated as contaminants in other diseases, as when they are found in the sputa of patients with known pulmonary disease, such as tuberculosis and carcinoma.[1] Before the era of modern therapy, patients with extensive visceral involvement due to *Candida* species were seen only occasionally. With the introduction of currently available drugs and therapeutic procedures, instances of such candidal infections occur with increasing frequency.

Advances in knowledge of the pathogenesis, clinical manifestations and management of candidiasis are being made. Herein is an attempt to summarize this knowledge from the point of view of the practitioner-internist.

Clinical Syndromes

In patients with localized candidiasis, such as oral, cutaneous, or vaginal infection, systemic disease may occur spontaneously but is more likely to be encountered in persons who have underlying diseases or those receiving predisposing therapies. In this presentation, systemic candidiasis refers to infection that predominantly involves one body system and is characterized by a constitutional reaction. Disseminated candidiasis, which refers to multisystem disease, may result from extension of either localized or systemic infection.

Systemic Candidiasis

Candidemia-fungemia due to *Candida* species is suggestive of disseminated disease or seeding of the bloodstream from a focus of significant visceral infection. However, in a number of cases, candidemia represents transient invasion of the blood, the elimination of which does not require systemic therapy. In other words, *Candida* may be cultured from the blood, but the subsequent clinical course of the patient, or the postmortem examination, indicates that established infection was not present.[2] In these cases, the transient fungemia may reflect such things as an infected intravenous catheter or antibiotic-induced floral changes with candidal overgrowth.

In patients who have persistent fungemia, especially those who have serious underlying disease, are receiving predisposing drugs, or have intravenous or indwelling urinary catheters, their clinical deterioration is the usual stimulus to consideration of therapy with amphotericin B. In some instances of persistent candidemia, examination of the patient's urine may reveal the pathogen before blood and urine cultures are reported. Because negative blood cultures have been noted in patients with disseminated candidiasis, the urine should be examined simultaneously for the presence of *Candida* in such cases. Because the kidney is the organ of maximal involvement in disseminated candidiasis, significant candiduria is not unexpected.[3,4]

Candidal Endocarditis—Approximately 75% of patients with endocarditis due to *Candida* species, unassociated with cardiovascular surgery, are believed to have preexisting valvular damage. Dick and Mullin[5] described a patient in whom the fungus was localized to the surface of an atrial myxoma. Candidal endocarditis after cardiovascular surgery has been rising steadily in incidence in recent years. The infection appears to be related to intravenous injections in most cases, but there is the possibility of direct access by the organisms to the heart valves at the time of cardiac surgery. Prior antimicrobial therapy and the trauma of cardiopulmonary bypass may be significant factors in the genesis of the infection. Although most instances of systemic and disseminated candidasis are caused by *C. albicans,* endocarditis in about half of the instances has been due to other strains of *Candida.*[6] The clinical manifestations of candidal endocarditis are usually similar to those of bacterial endocarditis, except for the more frequent occurrence of major embolic phenomena.

Such emboli have been reported in about 50% of cases and may reflect the characteristically large vegetations found at autopsy, which may have an area of as much as 5 cm. In some cases protracted, unexplained fever is the only consistent clinical finding. Petechiae and splenomegaly are usual. Blood cultures are not consistently positive in all cases. Candiduria and azotemia are infrequent. During treatment with amphotericin B, the infecting organism may grow in culture medium of hypertonic blood when there is no growth in ordinary blood cultures.[7,8] In one such case, small, beadlike, friable vegetations were found at operation instead of the larger vegetations commonly encountered in endocardial candidiasis.[8] Amphotericin B (Fungizone) is generally considered to be ineffective in the presence of an intravascular prosthesis, and it is recommended that the prosthesis be replaced if it is considered to be a focus of fungemia. In cases of refractory candidal endocarditis occurring in patients without such a prosthesis, it is also worthwhile to consider surgical intervention and removal of the valvular nidus of infection or even replacement of the valve.

Gastrointestinal Candidiasis — Candidal infections of the mouth not uncommonly spread to directly involve the pharynx, larynx, and esophagus.[9] Death from systemic candidiasis has been noted after dental surgery. Thrush in infants may be acquired in an epidemic fashion in the nursery, much like staphylococcal infections; it may also occur via the mother.[9] The usual treatment of this variant of the infection is to attempt to maintain concentrations of nystatin (Mycostatin) in the mouth, pharynx, and esophagus. However, in advanced disease, therapy with amphotericin B may be required.

Candidal esophagitis has occurred in the absence of candidiasis of the oral cavity. Retrosternal pain on swallowing, especially in patients receiving predisposing drugs, should bring this possible complication to mind. Characteristically, the barium-filled esophagus demonstrates lack of motility, decreased distensibility, increased retention of the contrast medium on the mucosal surface, and highly variable filling defects. In patients with candidal esophagitis, esophagoscopy may be dangerous because of the possibility of perforation.[10] The organism may be cultured from gastric aspirate and stool. Examples of gastric and duodenal candidiasis have also been observed.[3]

Because *Candida* organisms are part of the normal flora of the gastrointestinal tract, their presence in cultures of the stool may be difficult to interpret. However, in patients having certain underlying illnesses and receiving predisposing therapies, increased numbers of these organisms may provoke gastrointestinal irritation, usually in the form of diarrhea. Such a gastrointestinal focus may lead to significant fungemia. Especially in obese diabetics, overgrowing *Candida* may spread externally to involve the perineum and groin. Rectal candidiasis also has been observed.[3]

Pulmonary Candidiasis — Primary pulmonary candidiasis is rare, but the incidence of infection secondary to underlying diseases is reported to be increasing.[11] Pulmonary candidiasis may present as a mild recurrent bronchopulmonary infection with persistent and productive cough. Examination of the sputum reveals the presence of large numbers of budding yeast cells and pseudomycelia. Other patients may have more severe infection, and roentgenograms of the thorax may indicate consolidation and pleural reaction. Still other patients may demonstrate a miliary type of pulmonary infiltration and have associated fungemia. A definite diagnosis can be made by obtaining repeatedly positive cultures from bronchoscopic washings, by simultaneously culturing the organism from pleural fluid or blood, or by demonstrating *Candida* in biopsy sections of the lung. In disseminated candidiasis, the lungs are often involved, but the kidneys usually are the sites of maximal infection. When a diagnosis of pulmonary candidiasis has been established, the use of predisposing drugs such as antibiotics should be discontinued. With candidal bronchitis, no other therapy may be needed; if pneumonia is present, specific therapy will be necessary. Aerosolization of nystatin has been recommended in persistent milder infections.[12] Amphotericin B is required in more severe infections.

Genitourinary Candidiasis — Candidal invasion of the urinary tract is not infrequent in patients having underlying disease and receiving antibacterial therapy. In most instances of this variety, removal of the urinary catheter and cessation of antibacterial therapy are sufficient to halt the invasion. Of course, on occasion, such invasion is complicated by fungemia and even disseminated candidiasis. In disseminated disease, of whatever portal, the kidneys usually become the site of maximal infection. The concept has evolved that the tubular lumen provides a protected site for growth of the *Candida*, and evasion by the organisms of host defenses may be significant in the establishment of progressive renal infection.[3] In patients who are suspected of having disseminated disease, the urine, as well as the blood, should be cultured. Careful examination of the urinary sediment for yeasts may be diagnostic before reports of cultures become available.

Candidal balanitis and urethritis in the male have been reported. Treatment of the sexual partner may be required to prevent continued or recurrent infection.[9]

Candidal vulvovaginitis occurs when *Candida* species overgrow the vagina's normal bacteria, especially in diabetic women, pregnant women, and those receiving predisposing drugs. Among several forms of effective therapy, intravaginal use of nystatin, candicidin, or nifuroxime daily for two weeks or longer is usually successful. Vulvovaginitis associated with the use of oral contraceptives may not yield to treatment unless the use of "the pill" is discontinued.[13]

Intra-uterine infection of the fetus by candidal organisms, with resulting systemic candidiasis in the infant, has been reported by several investigators.[14-16] Although intrapartum contamination leading to cutaneous candidiasis is common, systemic infection in the infant is rare. A case of congenital systemic candidiasis is reported[16] in which the infant was born by cesarean section without prior rupture of the amniotic membranes. The route of infection is postulated to be either ascension of *Candida* from the mother's vagina and contamination of the amniotic fluid or hematogenous spread to the infant from the maternal focus. Cultures from multiple sites in the infant grow the organisms, with the lungs and kidneys being maximally involved.

Candidiasis of the Soft Tissues, Skeleton, and Central Nervous System—Postoperative wound infection due to *Candida* species has been complicated by candidemia.[2] Candidal cellulitis has been similarly complicated.[3] Candidal abscesses of multiple sites in the body, including the soft tissues, occur, but are usually encountered in patients with disseminated disease.

Candidal osteomyelitis may occur in patients with localized candidiasis elsewhere in the body.[17] Skeletal infections also may be noted in patients with disseminated candidiasis.

Both candidal meningitis and brain abscess have been encountered in patients without underlying disease and to whom predisposing drugs were not being administered. However, the increasing incidence of candidal infections of the central nervous system is undoubtedly related to underlying diseases and the use of predisposing drugs. An area of localized candidiasis elsewhere in the body, such as the skin or gastrointestinal tract, can be demonstrated in at least 50% of patients. Fever, headache, and vomiting are common presenting manifestations. Diplopia is not uncommon. Papilledema is frequent, and most patients have stiffness of the neck. More than one third have focal neurologic signs. In almost one half of the cases, *Candida* organisms are noted on direct examination of the spinal fluid. At autopsy, in about one third of the cases, visceral lesions, usually involving the kidneys, are found. In addition to amphotericin B therapy, drainage of brain abscesses is required.

Disseminated Candidiasis

Bogen and Kessel[18] reported the first case of disseminated candidiasis in an adult in 1937. Louria and co-workers[3] collected an additional 31 cases in persons more than 10 years old and pointed out that most of these cases have been encountered in the antibiotic-adrenal hormone era. Only about 20% of patients have disseminated candidiasis without having received prior antibiotic or corticosteroid therapy. Dissemination may occur in patients with localized areas of candidiasis in the gastrointestinal tract, skeleton, lungs, and other body sites. Disseminated candidiasis has occurred after dental extraction. At autopsy, the renal tissue is the site of maximal infection and abscesses may involve multiple regions, including the myocardium, brain, and lung. In this variant of the infection, the esophagus is the most frequently involved portion of the gastrointestinal tract, but gastric, duodenal, colon, and rectal involvement occurs.

Patients, Pathogens, and Portals

Patients afflicted with certain underlying diseases or conditions are particularly susceptible to systemic and disseminated candidiasis. These diseases and conditions include diabetes mellitus, hematopoietic disorders such as leukemia, malignancy, lupus erythematosus, rheumatoid arthritis, Cushing's disease, alcoholism, cirrhosis, severe burns, pulmonary alveolar proteinosis, uremia, malnutrition, postoperative states, pregnancy, hypocalcemia, Addison's disease, and certain states characterized by deficiencies in the gamma-globulins.

Patients receiving antibiotics appear to become more susceptible to candidiasis because of the suppressive effect of these drugs on members of the normal body flora, thus allowing overgrowth of other organisms including *Candida*. Adrenal corticosteroids so alter host defenses that patients receiving them also have increased susceptibility to candidal invasion. Use of radiomimetic drugs, immunosuppressive therapy, radiation, and surgical procedures also appear to decrease host resistance and enhance the likelihood of candidiasis.

Infections in man caused by species of *Candida* are usually due to *C. albicans*. *C. tropicalis* also produces systemic infection in man. Other members of the genus include *C. parapsilosis, C. pseudotropicalis, C. krusei, C. guilliermondi*, and *C. stellatoidea*. Excepting candidal endocarditis, these latter organisms rarely cause systemic or disseminated disease in man. About one half of the cases of candidal endocarditis are caused by members of the genus other than *C. albicans; C. albicans, C. parapsilosis*, and *C. guilliermondi* are the three organisms most commonly responsible for candidal endocarditis.

Preexisting mucocutaneous, gastrointestinal, and genitourinary candidiasis can be complicated by systemic or disseminated disease, especially if a precipitating factor, such as use of a predisposing drug, is supplied. The *Candida* may have direct access to the bloodstream through *prolonged use of intravascular catheters;* substitution of so-called scalp-vein needles may reduce the incidence of candidal infection via this portal. Frequent intravenous injections may provide a similar mechanism, and this is commonly operative in narcotic addicts in whom candidal endocarditis develops. Direct access to the heart valves at cardiac surgery may allow candidal implantation; the trauma of the operation and employment of cardiopulmonary bypass may enhance the likelihood of candidal endocarditis. An indwelling urinary catheter may likewise increase the possibility of candidiasis resulting from that portal. Rupture of a viscus, such as perforated diverticulitis coli may also result in systemic or disseminated infection. Surgical interruption of the gastrointestinal mucosa may eventuate in a similar chain of events.[3]

Clinical and Laboratory Findings: Some Generalizations

Fever is usual and characteristically remittent, and temperatures (oral) may range from 101 to 105 F. Shaking chills are noted in about 25% of patients, especially at the onset of fungemia.

A shock-like syndrome characterized by hypotension and oliguria occurs in about one third of patients at the time of fungemia.[3,19]

Petechiae and embolic phenomena, in the absence of candidal endocarditis, are uncommon in candidiasis.

Tachycardia and tachypnea are common but appear to be of no prognostic significance.[3]

In patients without underlying hematopoietic disease, leukocytosis and neutrophilia are usual. A normocytic normochromic anemia occurs in most patients.

Candida cells, if seen in the urinary sediment, may be diagnostic before the report of cultural data. Azotemia of variable degree occurs in about 50% of patients who do not have intrinsic renal disease at the onset of the infection. Of these patients, if therapy is unsuccessful, two thirds will have extensive renal candidiasis at autopsy. However, candiduria and azotemia are infrequent in candidal endocarditis.

In addition to the urinary sediment, other sources such as sputum or material from oral lesions and body fluids, when placed in a drop of 10% solution of potassium hydroxide under a cover glass and gently heated, may reveal the fungus.

It is to be stressed that isolation of *Candida* species does not per se indicate that the organism is necessarily causing disease. Such isolation may indicate either contamination from an exogenous source or habitation within the body in a commensal relationship without tissue invasion. Repeated isolation of the organism, or demonstration of it in tissue obtained by biopsy or autopsy, is a more exact basis for implicating the organism to be pathogenic. Isolation of *Candida* organisms from aspirates of closed-space infections such as abscesses or empyema, or from specimens of blood, urine, or spinal fluid more likely indicates significant infection. Pseudomycelia, especially their predominance over yeast forms on a smear preparation, may be more reliable evidence of infection than the presence of yeast forms alone. Examination of the buffy coat of a blood sample may reveal intracellular yeast forms and be helpful in the diagnosis of candidiasis, especially in patients in whom blood cultures are negative.[11]

Some Therapeutic Considerations

Antibiotic

The keystone of management of systemic and disseminated candidiasis is *amphotericin B*.[20-22] Although the mortality rate in patients with severe disease remains high, and despite the considerable toxicity of amphotericin B, it is the only effective and commercially available antimycotic agent having systemic effect. Patients with endocarditis, meningitis, or severe pyelonephritis are less likely to respond to therapy. In less severe infections, 25 to 50 mg of amphotericin B given each day intravenously for seven to 14 days may suffice. In more severe infections, higher daily doses should be given if the patient can tolerate them, and treatment should be continued four to six weeks.

Intrathecal or intraventricular administration of amphotericin B should be considered in patients with meningitis. Injection of the drug into other body cavities, such as the pleural space in patients having empyema, may have application. Amphotericin B has been given as an aerosol, applied to cutaneous and mucosal lesions, and injected directly into subcutaneous tumefactions and regions of osteomyelitis. It also has been given via arterial perfusion into an isolated limb and has been introduced into the lungs via endobronchial catheter.

Amphotericin B may be curative in candidal endocarditis that complicates cardiac operations. However, because the presence of foreign bodies (sutures, prostheses) may be implicated in the genesis of the lesion, cardiotomy with excision of vegetations and repair of any defect also is probably required. As noted previously, in endocarditis, unassociated with a prosthesis, surgical intervention and perhaps valvular replacement also may be considered.

Change Therapy

It is important to recall that infection, including fungemia, in some instances will resolve by change of intravenous tubing, removal of catheters or needles, discontinuance of predisposing drugs, and control of underlying diseases or conditions. Attention should be directed toward control of underlying diseases or conditions because the pathogenesis of systemic and disseminated candidiasis is intimately related to alterations in host resistance. Stringent efforts should be made to control malignancies, to correct malnutrition, to ameliorate blood dyscrasias, and to regulate diabetes mellitus and the like. The indications for such regimens as the glucocorticoids, cytotoxic agents, immunosuppressive drugs, antibiotics, and roentgen therapy should be reevaluated. Nonessential therapy should be discontinued, and other medications should be administered in the lowest dosage that is effective. Supportive measures including rest, improved nutrition, general hygiene, and care of the skin and mucous membranes are not to be neglected.

Surgical

Surgical intervention in nonendocardial candidiasis may also be an important adjunct. All foci of dead and devitalized tissues, sinus tracts, and fistulas should receive surgical consideration. Abscesses, empyema, and regions of osteomyelitis should be drained. Chronic pulmonary lesions may require resection.

Chemotherapy

Nystatin is employed for local effect against infections due to *Candida* species; the drug is poorly absorbed from the gastrointestinal tract. Treatment of candidiasis of the gastrointestinal tract, vagina, and infected cut-down sites has been successful. Oral and topical forms may be used adjunctively in the management of certain patients, if auto-reinfection from the intestinal tract seems likely. Although there is no indication that nystatin need be employed in the average patient receiving antibiotics, oral administration of the drug in an attempt to reduce the number of these organisms in patients with such diseases as diabetes mellitus, malignancies, and hematopoietic disorders may be acceptable.

The usual oral dose of nystatin is 150 to 300 mg (500,000 to 1,000,000 units) three times daily. In candidiasis of the mouth, pharynx, and esophagus, one tablet of nystatin (500,000 units) dissolved in the mouth four times daily is recommended. In milder pulmonary infections, a suspension of nystatin (50,000 units) in 40% propylene glycol in normal sodium chloride solution given as an aerosol in divided daily doses has been effective.[12] Use of nystatin vaginal tablets or suppositories containing 100,000 units once or twice daily is recommended in cases of vaginal candidiasis. For local use, a vehicle containing 100,000 units per gram is applied to the area once to several times daily.

Candicidin (Candeptin) is an antibiotic that is effective topically in cases of vaginitis. One tablet (3 mg) of candicidin or one applicator full (3 mg) of ointment is inserted high into the vagina twice daily, in the morning and at bedtime, for 14 days.

There are two nitrofurans that have antimycotic activity. A nitrofurfuryl methyl ether (Furaspor) is used topically. Nifuroxime (Micofur) is a fungicide that is combined with furazolidone in the preparation Tricofuron. Vaginal suppositories of Tricofuron are used once or twice daily until the *Candida* organisms are eradicated, when therapy is discontinued after an additional seven to 14 days. In addition, vaginal insufflation of the drugs in powder form may be carried out once or twice weekly, depending on the case.

Comment

Opportunistic candidal infections are increasing in incidence, reflecting the increased number of patients with impaired ability to resist candidal invasion, due to underlying disease, use of certain drugs, or employment of various therapeutic procedures. Physicians must be aware of the vagaries of systemic and disseminated candidiasis in order to initiate appropriate diagnostic procedures. Identification depends largely on sending pertinent material for microbiologic examination. Identification is mandatory, because effective therapy including amphotericin B, surgery, and control of the underlying disease can eradicate a significant number of opportunistic candidal infections.

There are selected patients in whom the possibility of systemic or disseminated candidiasis should come to mind, especially if clinical deterioration supervenes without more obvious cause. These include patients with a known locus of infection, such as gastrointestinal or genitourinary candidiasis. In such patients, a malignancy, hematopoietic disorder, cirrhosis, or a similar disorder that may impair host resistance can enhance the likelihood of extrafocal candidal invasion, further encouraged by use of venous or urinary catheters, surgery, antibiotics, glucocorticoids, radiomimetic drugs, and similar therapies that disturb the equilibrium between victim and invader.

In many patients harboring *Candida* species, the organisms represent an incidental finding and are of no critical significance in the course of the illness. In some, however, the organisms may be responsible for clinical deterioration. In some patients, candidal infection, including fungemia, will subside on use of such measures as a change in intravenous tubing, removal of a urethral catheter, or decreasing or discontinuing predisposing regimens. In other patients, heroic therapy, the keystone of which is amphotericin B, is required to eradicate the infection. Careful evaluation of the individual situation is the best approach to the dilemma of not advising unnecessary antimycotic therapy on the one hand and, on the other, avoiding failure to administer such therapy in patients with significant infection.

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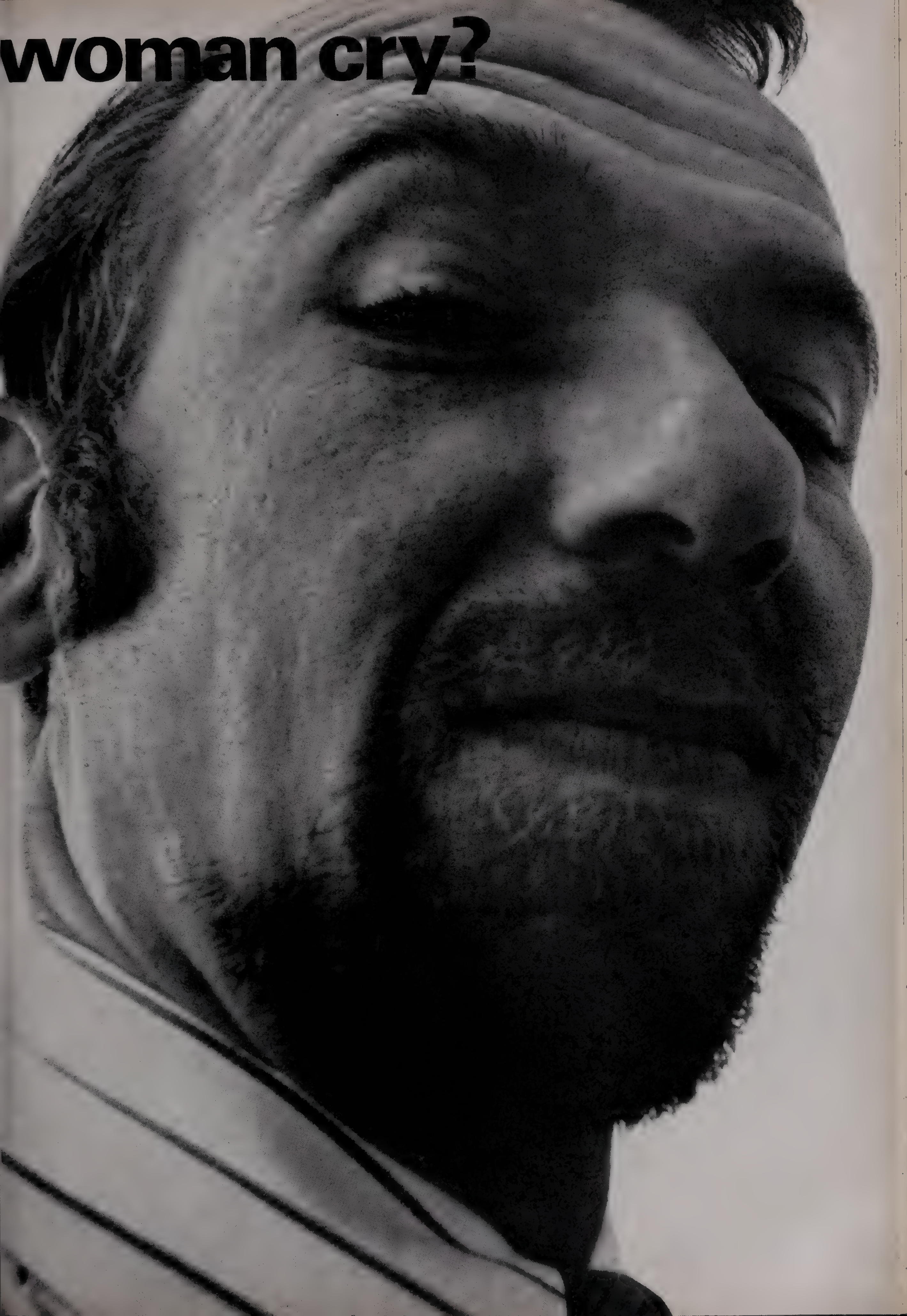

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Case Reports

Black Leadership-Potential Psychological Crisis

Black equality is growing in America. Initial advances of racial desegregation[4] are evolving into actual integration of the black and white communities. These advances proceed through government legislation such as the Supreme Court Decision (1954) and the Civil Rights Bill (1964). Black people are encouraged to participate in integrative efforts by both interpersonal and intrapersonal forces, and participation in this drive for equality may result in black casualties. Although physical violence is publicized (assassinations of Medgar Evers and Reverend King, Jr.), psychological damage can also result both to the black individual and to his cause. Two examples follow.

Case 1

This middle-aged black woman was born out of wedlock in a Southern city. Her mother later married; but when the patient was six years old her parents were divorced. Until age twelve she was raised by her mother who was severely crippled from polio. On her mother's death she was cared for by relatives until her marriage at age seventeen. Her husband, a previous divorcee, and she have now been separated for three years due to his infidelity. Within this period she has raised her large family with the aid of A.D.C. Her activities include membership in an Urban Coalition Group, board responsibilities for several community centers, and lecturer on Afro-American history to schools and private groups. Her interest in integration is encouraged by both black and white citizens. She is a high-school graduate and is on high academic standing after college attendance last year. When seen for treatment she reported feeling suicidal and "not happy;" her anxieties were apparent in her pacing, her thinly-veiled hostility, and her ambivalence. Her past history disclosed that she joined many integration groups, accepted responsible positions, and then shortly became inactive. She was unable to admit or show weaknesses to those about her. Despite vocally endorsing the groups, she openly admitted a preference to return to the South and to reside there. Her working diagnosis was passive-aggressive personality.

Case 2

This young black lady was born in the South and abandoned on a doorway when she was six months old. She was raised by an aunt, as "my mother was beautiful, selfish, and went off and left me." At age eighteen she married but for the last six months has been separated, due to her husband's infidelity. She has supported her children by employment, but increasingly considers going on A.D.C. Her job is connected with a University integration planning program, and though only a high-school graduate, she works very capably at this sophisticated level. Other posts include community center instructor and campaign organizer for black political candidates; both white and black friends sponsor her in these activities. In the initial interview she was in an agitated state: she could not remember what had happened the preceding day and was unable to talk about herself. Visible anxiety was noted as she trembled and withdrew from noise. Tears appeared easily. She did not want to let her employers and friends down, though she volunteered that her committee pressures led to her hospitalization. When last seen she was unhappy, frustrated, and talked of moving back to the South. Her working diagnosis was dissociative reaction.

Discussion

The above two women demonstrate the environmental and social disadvantages that often appear in a black family. Both were unwanted children, raised in a matriarchal setting, with inadequate father figures. Their parents' hostile relationships culminated frequently with projection of anger upon the daughters. Their early life was spent in communities which emphasized white supremacy and passive-dependent roles for black citizens.[3] The two women participated in juvenile, disastrous marriages to men who did not provide security, and both were left as single parents in unfamiliar surroundings.

Search for recognition helped direct these ladies into integration groups—particularly when they were encouraged by other people who recognized the leadership potential. Thus these women became energetic, productive workers in integrative efforts. They were well-liked and respected. Increased control and command duties were assigned them in recognition of their fine work. But soon group responsibilities exceeded emotional capacities. Attempts to handle personal and racial anger failed. Compartmentalization of identity,[1] denial, avoidance and projection were tried. Failure of these ego defenses increased anxiety, led to cancellation of integrative group efforts, and supported regressive wishes to return to the infantile state. Their exploitation as potential negro leaders inadvertently resulted in a decline of their self-esteem and goals. Feelings of failure brought the desire to return to the social setting and position occupied by their parents.

Treatment Resource

Government recognition of community mental health includes not only integration legislation, but also legislation providing direct community psychiatric care. The Hill-Burton Act promotes government financing of community mental health centers. These funds, plus extraordinary efforts of the medical community, created the newly opened St. Barnabas-Swedish Mental Health Center. The government funds obligate the center to community involvement by making its primary responsibility a specific community or "catchment" area. Its obligations are not only the treatment, but the prevention of mental illness.

Conclusions

The two case histories support a need for direct concern with the integration movement at a mental health center. Both black and white in their pressure to achieve racial equality may put such strenuous demands upon a black citizen either through sociocultural environment or because of individual personality factors,[2] that he may be limited in his ability to respond to this challenge. The integration movement can poorly afford to lose black citizens with clearly demonstrated capabilities.

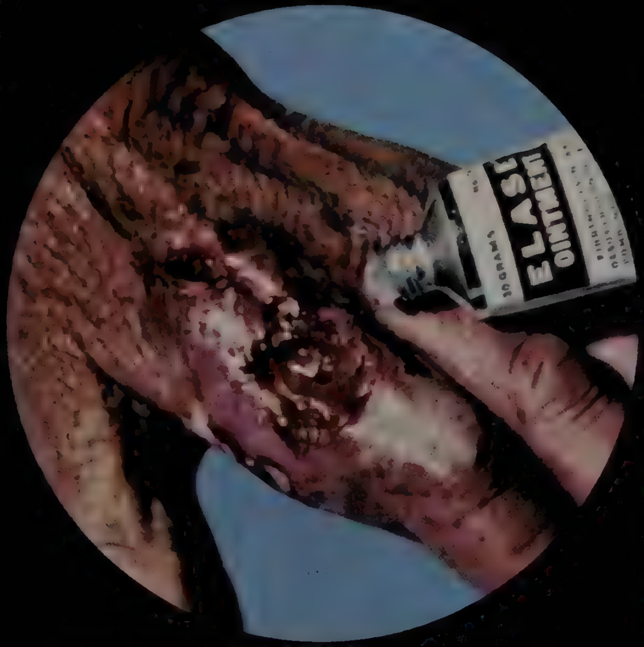
The nation, both black and white, should seek a gradual evolvement of community position for such people as the two women described above. The frenzy and pressure to achieve integration may deprive potential black leaders of personal happiness and the community of resourceful, responsible guidance.

The Mental Health Center is a potential help. First, it can provide inpatient or outpatient treatment for the frustrated community citizen pushed into areas of responsibility too rapidly. Second, the Center can provide an educative program within the community in hopes of preventing the above psychiatric casualties. It will be hoped that the St. Barnabas-Swedish Mental Health Center can rectify such tragedies as the above two case histories. A plan of community education, research, and clinical treatment by this health center can assist the legislated social concept of integration to become realized within our community in a manner non-destructive to participants.

William W. Brauer, M.D.
Minneapolis, Minnesota

References may be secured from the author or the reprints.

this ulcer did not heal...until its surface was cleared of dead tissue and debris



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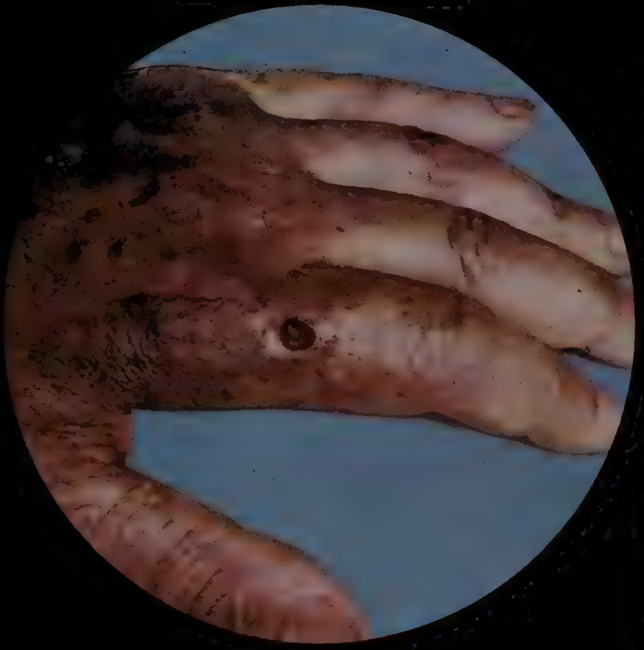

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References: 1. Danhof, I. E.: Report on file. 2. Hoon, J. R.: Arch. Surg. *93*:467 (Sept.) 1966.

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Adverse Reactions: *Gastrointestinal*—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. *Skin*—maculopapular and erythematous rashes; exfoliative dermatitis; photosensitivity; onycholysis, nail discoloration. *Kidney*—dose-related rise in BUN. *Hypersensitivity* reactions—urticaria, angioneurotic edema, anaphylaxis. *Intracranial*—bulging fontanels in young infants. *Teeth*—yellow-brown staining; enamel hypoplasia. *Blood*—anemia, thrombocytopenic purpura, neutropenia, eosinophilia. *Liver*—cholestasis at high dosage.

Upon adverse reaction, stop medication and treat appropriately.

Lederle

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P
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The go-ahead-and-enjoy-your-vacation summer cold and allergy pill.

Novahistine LP lets you provide effective relief of summer cold and allergy symptoms, lets your patients go ahead and enjoy their vacations.

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DOW

Dermatology

Verruca Vulgaris

RECENT ELECTRON microscopic studies of human wart tissue have demonstrated the probable viral nature of this lesion. In the earliest stages of infectivity, viral particles are seen in the nucleus of the cells of the upper layers of the epidermis (stratum malpighii, granulosum, and corneum). Their size has been stated to be approximately 50 millimicrons. Interestingly, no viral particles have been observed in the lower layers of the stratum malpighii or basal cell layer. The viral particles are first arranged within the nucleus in regular or crystalline formations. Later the particles are dispersed within the nucleus and cytoplasm of the infected cell. These findings tend to correlate with the observations of light microscopy in which basophilic intranuclear inclusions are seen. Feulgan* reactivity would indicate that the central core of the virus contains DNA. The human wart virus has been classified as a member of the Papova virus group.

Immunology

Antibody (rabbit) has been observed in complex with human wart virus. Both pooled human gamma globulin and serum from patients with warts have been found to contain antibodies to wart in low titre. The weak response of the host can be attributed to the relatively inaccessible location of the virus (upper layers of the epidermis) with respect to the antibody-forming cells of the body.

Clinical

On the basis that there is an antibody response to human wart virus (albeit low) three clinical stages have been described. The first stage, which is most common in children, is characterized by the primary infection followed by the occurrence of additional lesions, presumably through auto-inoculation. In this stage there is little resistance (antibody titre). Removal of warts during this period is associated with a high rate of recurrence. In the next stage partial resistance develops and the spread ceases. However, resistance is not such that the wart disappears. Removal at this stage results in fewer recurrences. Finally, in the third stage, resistance increases to the level where the wart disappears.

It should be pointed out that the foregoing statements are not without controversy. Studies are continuing on this problem and perhaps the nature of infectivity and spread will be further clarified in the not too distant future.

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Minneapolis, Minnesota

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*See Test Your Word Score Page 933.

Missed Abortion of a Twin

If, in a woman pregnant with twins, either of her breasts lose its fullness, she will part with one of her children; and if it be the right breast which becomes slender, it will be the male child, or if the left, the female.*

---

*Hippocrates

Review

Placental Localization*

PLACENTA PREVIA is a serious complication of pregnancy that can occur with painless third trimester bleeding *and* malpresentation. According to Hibbard[1] an oblique or transverse lie, an eccentric fetal pole, or an excessively high vertex or breech, are not absolute clinical criteria for the diagnosis of placenta previa since only one third of patients with third trimester bleeding or malpresentation, or both, have placenta previa. The diagnosis may be directly made by means of vaginal examination in which the placenta is felt through the cervical os; but such examination should be done only in the operating room, where preparations have been made for immediate blood infusion and cesarean section in the event that hemorrhage occurs. This "double set-up" examination should not be done prior to 37 weeks' gestation, when the threat of prematurity exists, unless the quantity of blood being lost is excessive enough to dictate immediate termination of the pregnancy. Hence other means are necessary before 37 weeks to localize the placenta when loss of blood is not excessive.

Without placental localization, many of these preterm patients with third trimester bleeding not due to cervical or vaginal lesions might conceivably be hospitalized for the remainder of the pregnancy. Thompson and co-workers[2] estimated that three out of 100 hospital beds could be used for other purposes if the possibility of placenta previa could be excluded in these cases. Accurate localization of the various types of placenta previa has led to better management of the patient at delivery, with a resultant decrease in fetal and maternal mortality. Placental localization may also be indicated prior to amniocentesis and intrauterine fetal transfusion to avoid needle trauma to the placenta. Several of the localization techniques to be described are pictorially represented in the Figure.

Soft-Tissue Placentography

In 1934 Snow and Powell[3] first described visualization of the placental shadow with soft-tissue x-ray technique. Using anteroposterior and lateral views they found that the thickness of the uterine wall was relatively constant before labor; the placenta could be localized as an area of crescentic thickening of the uterine wall. With this technique they correctly localized the placenta in more than 90% of their cases. Some investigators noted difficulty with this technique when it was discovered that the amniotic fluid and the placenta have the same degree of radiologic densities and that errors could occur if accumulation of amniotic fluid was superimposed over soft tissues, giving the mistaken impression of the placental shadow. Tomography† has been suggested in these instances but has not been used because of the excessive radiation exposure to both the mother and the fetus.[4]

Contrast Cystography

Ude and associates[5] initiated the combined use of the soft-tissue technique and positive-contrast cystography. The relative thickness of the uterine wall between the fetal pole and the dome of the opacified bladder was measured, and if this thickness was greater than 2 cm, the presence of placenta previa was suspected. If the dome of the bladder was indented by the fetal pole, the possibility of placenta previa could always be excluded except for posterior placenta previa. In this case, a lateral pelvic roentgenogram was required. Negative-contrast study has been advocated, with the use of 200 to 300 ml of air injected into both the bladder and the rectum, to better visualize soft-tissue uterine densities and in cases of hypersensitivity to the iodinated dyes.[6]

Although the soft-tissue technique and cystography is an indirect means of localizing the placenta, visualization of placental calcification will directly localize its position. The calcification appears as finely or coarsely granular densities. Various studies reported visualization of placental calcification in vivo in from 31 to 50% of the cases at 32 to 36 weeks' gestation, with increasing chance of visualization as term approaches.[4]

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*This paper was prepared under the supervision of members of the faculty of the Mayo Graduate School of Medicine.

†See Test Your Word Score Page 933.

Gravitational Placentography

In 1949, Reid[7] devised the method of gravitational placentography. Films were taken with the mother in the erect and the semi-erect position, allowing the fetus to gravitate into the lower uterine segment. Displacement of the fetal pole from certain regions of the maternal pelvis could thus be measured. The minimal distance between the presenting part and the sides of the pelvic inlet should be slightly greater than the thickness of the uterine wall. Reid estimated that the thickness of the lower uterine segment was not greater than 1.5 cm. An anteroposterior view is taken with the mother in the semi-erect position and a lateral view is taken in the erect position. Indirect localization of a placenta previa could be made if the following findings were present:[8] for *anterior placenta previa,* (1) anterior placental shadow (lateral view), (2) fetal head (pole) displaced more than 2 cm from pubis (lateral view), with or without lateral displacement (anteroposterior view); for *posterior placenta previa,* (1) posterior placental shadow, (2) fetal head (pole) displaced more than 2 cm from promontory, with or without lateral displacement; for *lateral placenta previa,* (1) lateral displacement of fetal head (pole), (2) presenting part may be within 2 cm of pubis or promontory.[8] A *posterior placental* shadow may not be visualized, owing to the increased density of the patient's body along the posterior wall of the uterus. If displacement of the fetal pole from the promontory is greater than 2 cm, a lateral view is taken with the mother semi-erect. If the pole falls into the posterior aspect of the pelvis, the possibility of posterior placenta previa is excluded.

Before this technique can be used, the physician must rule out the presence of a full bladder or rectum, pelvic masses, bony abnormalities of the pelvis, and a lax abdominal wall, which allows the fetal head to float. The accuracy of the technique is less with breech presentations, with transverse lies, and previous to 32 weeks' gestation. Reid excluded the possibility of placenta previa in more than 90% of his patients suspected of having it; however, in 44 patients with placenta previa diagnosed, he could confirm only 73% at delivery. Schreiber and Red[9] believe that this technique is accurate only when the placenta is normally situated, and that more direct methods of placental localization have now replaced soft-tissue placentography as the method of choice.

Amniography

Amniography, as developed by Menees and associates[10] primarily for the use of placental localization, was reported in 1930; but the contrast materials used at that time were frequently too toxic and caused premature labor. In addition, the possibility of needle injury to the fetus and its blood supply resulted in the relative disuse of this technique. With the perfection of the technique of amniocentesis and the development of newer, less toxic contrast materials, amniography became an acceptable procedure.

Technique

With the technique of amniocentesis, 30 to 50 ml of amniotic fluid are withdrawn and replaced with an equal amount of contrast material. Thirty minutes later an anteroposterior roentgenographic view of the pelvis is taken; if the placenta cannot be localized, a lateral view is taken. The placental edge can be seen as a filling defect where there is a disruption of the smooth outline of the amniotic sac. The placenta often shows small, rounded projections: the fetal surface vessels. Occasionally the cord can be seen if it is coated with dye. The possibility of placenta previa can be excluded if the fetal head is found in close contact with the smooth outline of the amniotic sac.[11]

Results

With this technique, the placenta can be localized before 32 weeks' gestation in patients with antepartum bleeding. Blumberg and coworkers[11] were able to differentiate low-lying, partial, and complete placenta previa. Although an indirect method, the technique has greater than 97% accuracy, with no false-positive results.[11,12] In a double-blind study of 30 patients in whom both the soft-tissue technique and amniography were used and in whom the location of the placenta was determined at delivery, three radiologists reviewing all the films made a total of 29 errors with the former method and only three errors with amniography.[13] Amniography will also reveal uterine deformities and tumors, soft-tissue anomalies of the fetus, hydatidiform moles, mono-amniotic or di-amniotic twins, fetal sex, and fetal viability.[14] Berner[13] and Blumberg and associates[11] did not incur any maternal or fetal complications with amniography.

Arteriography

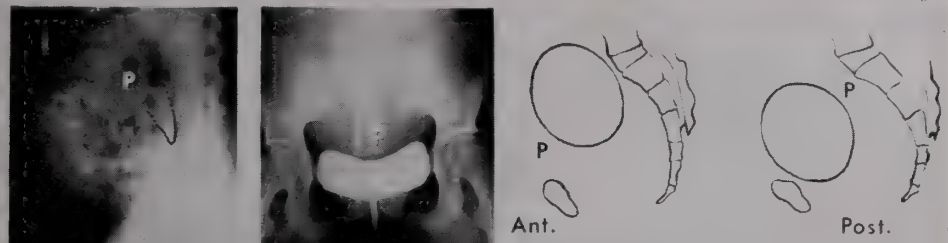
In 1929 Dos Santos[15] performed a translumbar aortogram for placental localization, and in 1952 Sutton[16] did the first retrograde femoral arteriogram for the same purpose.

Sedlinger Technique

After the femoral artery is punctured, a guide wire is passed through the needle into the external iliac artery, and the needle is withdrawn. A plastic catheter is then passed along the guide wire 20 to 24 cm to the distal portion of the aorta, above the bifurcation. The position of the catheter is then determined by fluoroscopy.[14] While the femoral arteries are compressed, 20 to 70 ml of contrast material are injected into the catheter, and roentgenograms of the pelvis are taken. Sutton[17] suggested that only one lateral view of the pelvis is needed, and during his procedure, the external os is marked with a vaginal speculum. Schreiber and Red[9] obtain a two-second film for the arterial phase and four-second and six-second films for the placental phase. Hedberg and Rådberg[18] take four anteroposterior views at varied intervals.

Results

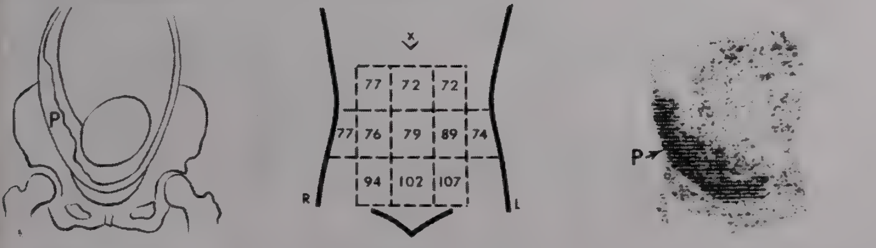
Hedberg and Rådberg[18] defined the upper border of the lower uterine segment as a line between the promontory and 4 to 5 cm above



Soft-tissue Placentography

Cystography

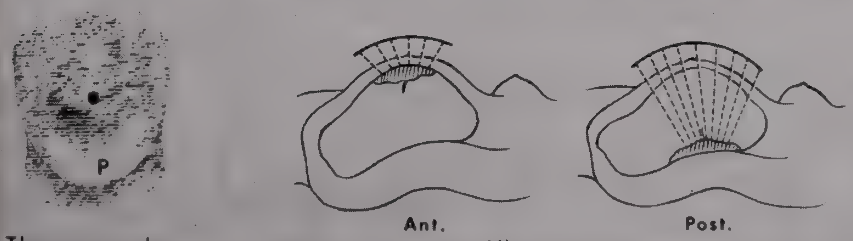
Gravitational



Amniography

Radioisotope tracing

Radioisotope scanning



Thermography

Ultrasonic

Figure—Techniques for placental localization.

the symphysis. The placental sinusoids are visualized as fluffy, white opacities; if none are visualized below the upper border of the lower uterine segment, the possibility of placenta previa can be excluded. A low-lying placenta exists when the sinusoids are present 3 to 4 cm below this border. As an aid in localizing the placenta, the internal os is located at the level where the uterine arteries, during the arterial phase, turn upward along the lateral margins of the uterus. If the opacities cover the area of the os, a total previa exists; if they are between this area and the one for a low-lying placenta, a partial or marginal placenta previa is present. Hedberg and Rådberg advocated the use of stereo films in the anteroposterior view to differentiate anterior and posterior placentas, or the use of a lateral film after a second injection.

In several studies[17-19] there was a 100% accuracy in localization, with no significant complications. The procedure can be done as early as eight weeks' gestation and can be used to diagnose other conditions such as ectopic or abdominal pregnancy, fibroids, and moles. Obesity, malpresentation, and hydramnios have no effect on the accuracy of this technique; however, the procedure is contraindicated in patients with hepatic or renal disease.

Intravenous Placentography

After the arm-to-tongue circulation time is determined, 75 ml of contrast material are rapidly injected into the antecubital vein. Two seconds plus the circulation time after the injection, an anteroposterior film of the pelvis is taken. Placental sinusoids appear as "cotton-ball" densities, and the placenta is easily viewed if it lies in the fundus or laterally, where the tangential view allows overlap of the sinusoids. Schreiber and Red[9] and Hendrick and Schreiber[20] found that intravenous placentography was more than 95% accurate; however, they were unable to differentiate a marginal placenta previa from a low-lying placenta. With a marginal previa, the sinusoids cover the fetal head, but with a complete placenta previa, there is less overlap of the sinusoids on the fetal head because of its displacement by the placenta.

This simple technique is accompanied by no complications and allows direct visualization of the placenta, though the roentgenograms are more difficult to interpret.

Isotopic Placentography

Radioisotopes were first used for placental localization in 1951 by Browne,[21] who used radioactive sodium (^{24}Na). Because of the short half-life and the rapid loss of this untagged substance from the blood into the tissues, ^{24}Na was regarded as a poor tracer. In 1957 Weinberg and co-workers[22] improved this technique, using radioactive iodinated serum albumin (RISA-131). With this material, the placenta can be localized in an area of increased radioactivity owing to the increased flow of blood to the placenta and the pooling that takes place there in relation to the surrounding structures.

Technique

At the Mayo Clinic the supine patient is given 5 μc of radioactive iodinated serum albumin-131 intravenously, and 10 minutes are allowed for dispersal of the material in the blood. A scintillation counter first records the gamma radiation over the precordium, which serves as a base line, and then over the uterus anteriorly. The abdomen is divided into 11 segments: three upper fundal, three miduterine body, three lower uterine, and one in each flank. The counter records the number of gamma emissions per minute from each segment, and the emissions are reported as counts per second for easier comparison. Other investigators record the counts as a percentage of the precordial count, and Hibbard[1] believes that the counts over the placenta ideally should be 1.5 to two times that of the surrounding uterus. Shanabrook[23] records each segment for one minute and then reverses the order and again counts the segments. The two counts for each segment are averaged and expressed as a percentage of the precordial count. The highest and lowest segments are averaged, and any segment that has a percentage count above this average represents the area of placenta.

Visual depiction of the placenta by scanning appears to be more anatomically correct than by scintillation, but this has not resulted in a greater clinical accuracy. Although more direct evidence of localization is present with the scan, more time is required for its recording and a larger dose of radioactive material is needed.[24]

Radioactive Substances

The ideal radioactive substance must remain in the blood for a reasonable length of time so that the recording can be done. Yet beyond this time, the rapid elimination of the radioactive material is desirable to keep the radiation exposure at a minimum. Human serum albumin is the preferred carrier substance because it is easily labeled, its metabolism is understood, and it does not cross the placenta in significant amounts. However, the use of albumin as a carrier modifies the rate of excretion of the isotopes from the body so that only seven to 10% are lost each day. The radioisotopes in current use for placental localization are radioactive iodinated serum albumin-131, 132 and 125, chromium-51, and technetium-99m.[19] Both radioactive iodinated serum albumin-131 and 125 dissociate into the free form, and the fetal thyroid must be protected with an iodine block by the administration of 10 drops of Lugol's solution several hours before the procedure and one day after the procedure.

Radioactive iodinated serum albumin-131 is easily produced and stored, and is commercially available. Because of its relatively long half-life of eight days, it can be given only in small doses of 5 μc. Also it emits beta rays, which are not recorded by the scintillation counter and which serve to increase the radiation hazard.

Radioactive iodinated serum albumin-125 must also be given in doses of 5 μc because of its long half-life of 60 days, but it is considered superior to radioactive iodinated serum albumin-131 because it is a pure gamma emitter.[1]

Radioactive iodinated serum albumin-132 has a half-life of only 2.3 hours and, as a result, can be given in higher doses, ranging from 50 to 100 μc. No block is required because of the short exposure time to radiation. However, it is not commercially available and has to be prepared prior to the test; in addition, it emits beta radiation.

Chromium-51 can be tagged to albumin or erythrocytes. The patient's own erythrocytes are used, and the tagging preparation takes about one hour. If an emergency situation arises, banked, tagged blood that is group O and Rh negative can be used; such blood has the advantage of not crossing the placenta, and no preparation or block is necessary. It has a half-life of 27.8 days and can be given in a dose of 20 μc.[1]

Technetium-99m promises to become the most effective tracer substance. It is a pure gamma emitter, has a half-life of six hours, and can be administered in doses of 200 to 500 μc without the use of a preliminary block. Because such a high dose of radioactivity can be given, the scanning technique can be used.[25] However, the substance must be prepared prior to the test, and most hospitals do not have the proper isotope facilities for this.[1]

From a genetic standpoint, all radiation is potentially dangerous. It is cumulative and there is no lower limit of exposure that is safe. According to Hibbard,[1] the various x-ray methods of placental localization produce a considerable amount of radiation exposure to both the fetal and maternal gonads. If two roentgenograms of the pelvis are taken, the fetal and maternal gonads each receive an exposure of 1,000 mrems. One of the main advantages of isotope placental localization is the considerably smaller radiation exposure. With the recommended dosage of the various isotopes, the calculated radiation exposure to the fetal and maternal gonads ranges from 0.5 to 15 mrems.

The results of isotope placentography have been excellent; the accuracy ranges from 93 to 100%.[1,2,25-27] In most studies there were no false-positive results. Inaccuracies result from difficulty in localizing posterior placentas, whether normally or abnormally situated. Weinberg and associates[28] reported that high counts in the flanks are suggestive of a posterior placenta. Some investigators recommend either a vaginal[29] or a perineal[23] recording to localize a posterior placenta previa. Others advocate a lateral scan.[30] False-negative results occur because of the difficulty in distinguishing a low-lying placenta from a marginal placenta previa.

Thermography

The increased vascularity and metabolic activity of the placenta produce more heat than do the surrounding structures, and this heat is conducted directly to the skin overlying the placenta. The increase in infrared radiation, which is a function of the temperature, can be recorded in less than five minutes in the form of a two-dimensional thermoplacentogram: a technique entailing the use of specialized, expensive equipment.

Birnbaum and Kliot[31] reported an error of only 3.7% in localizing the placenta in their study of 53 patients. Others are not as enthusiastic, citing the technical difficulties and expense of the procedure and the difficulty in localizing posterior placentas.[9,14,32,33] Some believe, however, that this method is only in its infancy, that more work must be done to refine the technique, and that the method has promise as a useful procedure for placental localization.

Ultrasonic Placentography

Localization of the placenta using ultrasound is based on the Doppler principle: the ultrasound waves directed into tissue are reflected off surfaces and are recorded by a transducer. When these waves are reflected from a moving target, the frequency is changed; it is amplified, filtered, and converted either into an audible signal or into a visible one as recorded by an oscilloscope.[34]

Motion of the fetal heart and blood flow in the cord, placenta, and the maternal and fetal vessels can be detected. Each has its own characteristic sound, including the placenta. Location of the "placental sound" will establish its position.[35] With the patient supine, the abdomen is divided into nine segments, and each segment is searched with the transducer. When the placental sound is found, it is possible to determine whether the placenta is anterior or posterior. If anterior, the echo waves are confined to a small area; if posterior, the echo waves are scattered and recorded over a wider area because of the distance between it and the transducer. In addition, a posterior placenta may be suspected if there is loss of parts of the placental sound over this wide area because of the interposition of the fetal body or small parts. Maternal blood flow can be distinguished from fetal blood flow by the difference in heart rate; maternal arterial sounds are synchronous with the pulse; and maternal venous sounds, although they vary, can be identified when they are obliterated, with an increase in the intra-abdominal pressure.[34]

This technique actually does not localize the placenta but rather localizes the point where the cord inserts into the placenta. Thus the margins of the placenta cannot be localized. The distance between the placental edge and the cord insertion depends on the size of the placenta, which is essentially a function of its age. Brown[34] calculated that the placental diameter, starting at 15 to 19 weeks' gestation, is 10 cm and increases 2 cm every four to six weeks, to a maximum diameter of 18 cm at 34 weeks. Assuming that most cords are eccentrically inserted into the placenta, one can estimate the distance of the placental edge from the cord by taking 60% of the diameter at that gestational time and using this figure as the overall radius of the placenta to obtain the theoretic placental margin.[34]

A new technique in ultrasound recording has been described in which the entire anatomic area is scanned and the sounds are recorded by the oscilloscope and converted into one composite picture. The placenta is visualized in cross section as a thin but compact area of multiple echoes or small white dots appearing beneath the outline of the uterine wall. Taking pictures at 2-cm intervals in both the horizontal and the sagittal plane makes it possible for the location and boundaries of the placenta to be plotted graphically.[36] These investigators hypothesized that, with refinement in technique and equipment, placental abnormalities such as marginal sinus separation and circumvallate placenta can be diagnosed.

Brown,[34] using the Doppler ultrasonic technique, obtained an accuracy of 91%; Gottesfeld and associates,[36] using the composite oscilloscope method, found a correct diagnosis in 97% of their cases. This ultrasonic technique is comfortable for the patient, has no side effects or radiation hazards, can locate the placenta at 20 weeks' gestation, and can be used serially throughout the patient's pregnancy.

Conclusion

The proponents of each of the various techniques of placental localization stress the safety, accuracy, and simplicity of their methods. Because the accuracy of most of these techniques is generally better than 90%, it is difficult to say which one is the best. All have certain advantages and disadvantages which must be considered when a method for placental localization is selected. Factors to consider are: direct-versus-indirect localization, cost of equipment and availability of facilities, ease to patient and preparation required, technical skill, radiation hazard, complicating factors (obesity, hydramnios, breech), gestational time, contrast-media hypersensitivity, and duration required for technique in emergency situations.

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Science

Science must have a heart as well as a head. Science must be understood for what it is—an instrument, and only that, which the mind of man had conceived for quarrying into the unknown. But it is not a deity. No civilization has ever endured in which science had no objectives but its own deification. No civilization has ever endured in which scientific progress was without a moral equivalent.*

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*Mabel Studebaker, School Life.

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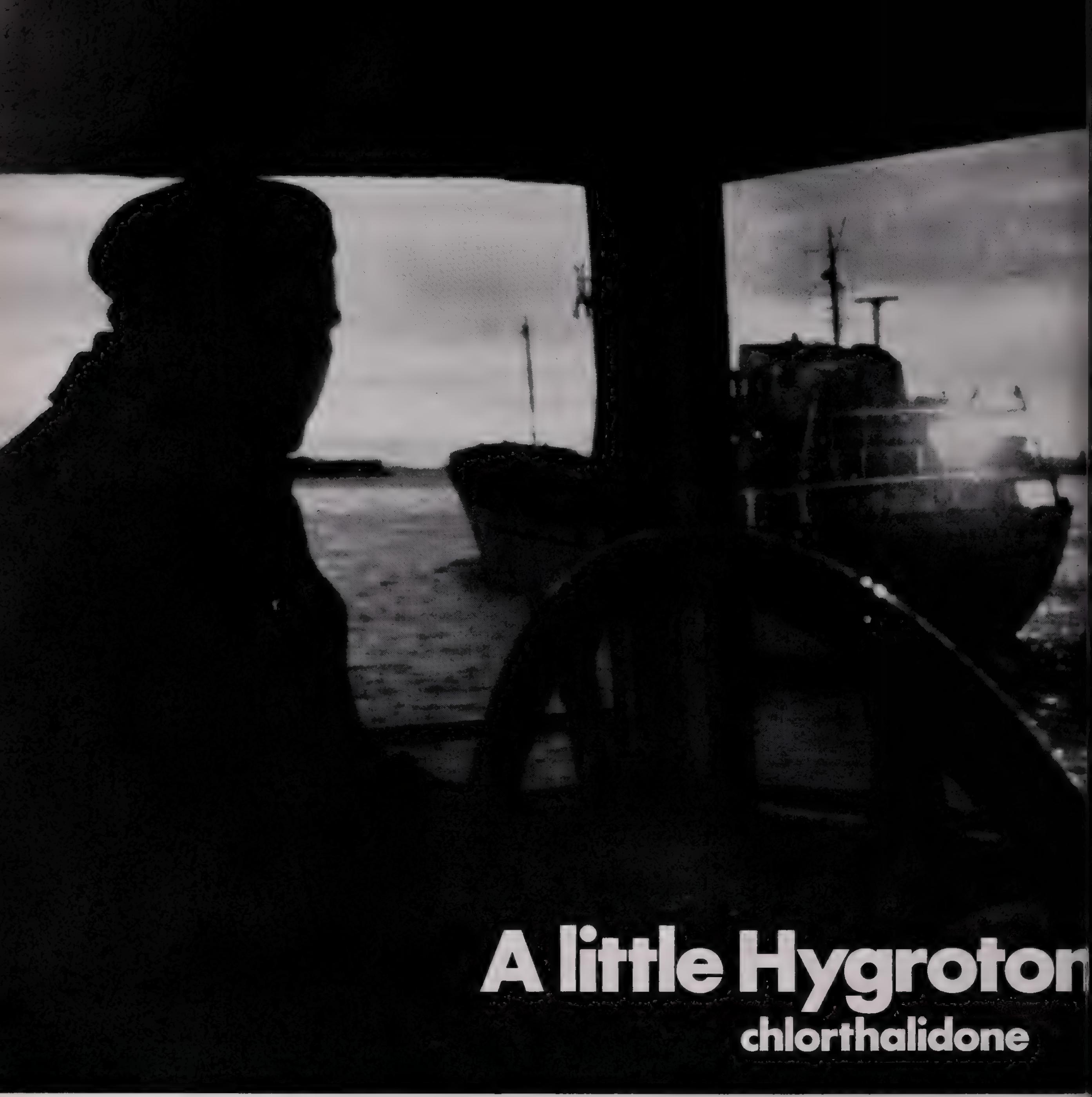
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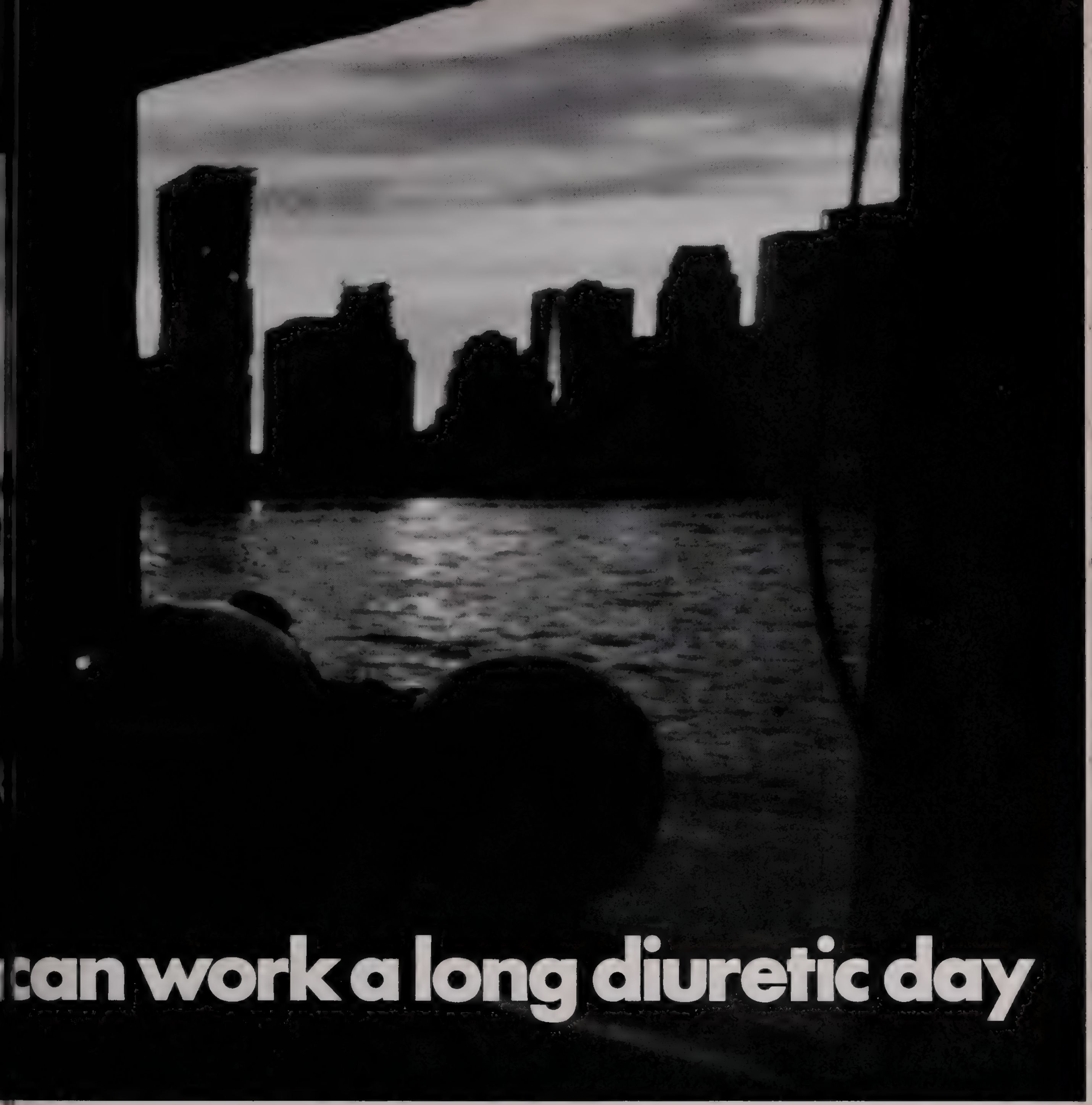

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Grand Rounds

Needle Biopsy of the Parietal Pleura*

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In 1954 Sutliff et al. called attention to the diagnostic efficacy of open pleural biopsy in the diagnosis of pleural diseases associated with pleural effusions.[1] This was soon followed by adaptation of the Vim-Silverman needle to biopsy of the parietal pleura by DeFrancis et al.;[2] and since 1955 it has been repeatedly demonstrated that needle biopsy of the parietal pleura is an important means of diagnosis of tuberculous and malignant pleural effusions.[2,20]

It soon became evident that the Vim-Silverman needle had at least one serious disadvantaged that militated against its routine use for pleural biopsies; an adequate specimen is frequently not obtained.[17,19] In addition, it is potentially dangerous, especially when there is little or no pleural effusion, because of the likelihood of removing a core of lung tissue at the time of biopsy. It is also reported that there is considerable distortion in the histologic appearance of the specimen.[20] These difficulties stimulated the design and manufacture of six new needle biopsy instruments.[23,24,15,25,26,27] In 1958 Abrams[24] and Cope[15] each introduced blunt-end needles especially designed to biopsy pleura. Since their introduction many authors have stated their preference for blunt-end needles.[13,19,20,17,10] The Cope needle appears to have gained wider acceptance in the United States, whereas the Abrams (Harefield) needle has been more widely used in Britain and Europe.

Methods

The purpose of this paper is to review our experience with blunt-end needle biopsies of the parietal pleura and to compare it with the experience of other physicians and institutions.

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*Presented as a Medical Grand Rounds at Hennepin County General Hospital, December 19, 1967.

The records of the Hennepin County General Hospital Department of Pathology for the period 1 January, 1965, through 1 December, 1967, were reviewed. All specimens entered as "pleural biopsy" were noted and the name and number of the patient recorded. Pathology reports of all pleural needle biopsy specimens were reviewed and the slides reinterpreted by a staff pathologist.

The charts of all patients thus selected were reviewed, and the final diagnosis establishing the etiology of the pleural effusion was determined, utilizing histologic or bacteriologic evidence whenever possible. Autopsy results were also evaluated whenever available. In some patients the final diagnosis was based on clinical grounds.

The techniques employed in obtaining pleural biopsies were those described by Cope[15,19] and Abrams.[24] The post-biopsy x-ray reports and physicians' progress notes were reviewed on all patients to discover any complications of the biopsy.

Case Reports

Case 1

An 84-year-old white male was admitted to the Medical Service with complaints of weight loss and weakness of three weeks' duration. He was a vague historian but had apparently been well until the onset of weakness, which was especially marked in his legs. He had not been out of bed for the two weeks prior to admission. He was a non-smoker. A chest x-ray on admission showed a right pleural effusion but no evidence of cardiomegaly or congestive heart failure.

Physical examination revealed a well developed, elderly white male. Breath sounds were decreased over the right lower hemithorax posteriorly, and there was dullness to percussion over the same area. The temperature was 98.6°; blood pressure 170/80; pulse 80. Hemoglobin on admission was 12.3, white blood count 5,600 with a normal differential. Thoracentesis was performed one day after admission. Four hundred cubic centimeters of serous fluid were withdrawn: 3.2 grams of protein, sp. gr. 1.027, white blood count 400 with 86 mononuclears, 14 PMN, red blood count 11,000. Culture and smear were negative for tubercle bacilli and also for malignant cells. Sputum culture grew out Pseudomonas. Circulation time, arm to tongue, was 24 seconds. Fungus skin tests were negative. Intermediate strength purified protein derivative skin tests on two occasions were read as negative. A second strength purified protein derivative was likewise reported as negative. Circulation time repeated one week later was 18 seconds. Prothrombin time was 14.9 seconds and partial thromboplastin time 41 seconds. One week after admission, a pleural biopsy was performed with the Cope needle, along with the withdrawal of 500 cc. of serous fluid. The pleural biopsy reported: "Several distinct granulomas are seen which contain epithelioid cells and some giant cells of the Langhans type, 'consistent with tuberculosis'."

The patient was transferred to the Adult Isolation Service; a repeat intermediate strength purified protein derivative was positive with 9 mm. induration at 48 hours. Multiple sputum specimens were negative for acid-fast bacillus on smear and culture, as was the pleural fluid. The patient was begun on Isoniazid 300 mg./day and pyridoxine 25 mg./day and was transferred to Glen Lake Sanitarium.

Case 2

A 57-year-old white male was admitted to the Adult Isolation Service with a chief complaint of chest pain and dyspnea of three weeks' duration. He was noted to have a pleural effusion on the right when an admission chest x-ray was obtained in Emergency Receiving. His past medical history included hospitalization at Glen Lake Sanitarium some 15 years previously for pulmonary tuberculosis, and a more recent diagnosis of chronic obstructive lung disease and bronchiectasis. He was a heavy smoker.

Physical examination on admission revealed a dyspneic white male with a respiratory rate of 40, blood pressure 146/86, pulse 90 and temperature 102° F. There was very extensive clubbing of the fingers and toes. Decreased breath sounds and dullness to percussion were noted at the right base posteriorly, extending up to T-7; and a Grocco's triangle was present on the left. The liver was down three centimeters below the right costal margin. Admission x-ray revealed a right middle lobe, right lower lobe infiltrate and a large right-sided pleural effusion. His admission diagnosis was pneumonia with effusion. Sputum culture grew pneumococci. Hemoglobin was 15.8; white blood count 13,800 with a shift to the left.

On the day of admission 1,000 cc. of serosanguineous pleural fluid was removed from the right chest: sp. gr. 1.015, protein 2.9 grams, cell count 2,300 with 87 PMN and 13 monos. RBC was 40,000/cu. mm. Prothrombin time was normal. Multiple thoracenteses were performed with an average of 2,000 cc. of serosanguineous pleural fluid being withdrawn every two or three days. One week after admission a pleural biopsy was performed with the Abrams needle and reported as "benign, with fibrosis." Pleural fluid was negative for malignancy on two occasions and suspicious for malignancy on three occasions. Two weeks after admission a bronchoscopy was performed with multiple negative bronchial biopsies and negative bronchial washings. A second strength purified protein derivative was positive; multiple sputum and pleural fluid cultures were negative for acid-fast bacillus. Repeat pleural biopsy was done three weeks after admission and reported as showing "metastatic invasion of the pleura, primarily thought to be a bronchiogenic carcinoma, possibly a small cell carcinoma." Chest tubes were placed and HN_2 was instilled, which controlled the effusion and gave the patient considerable relief of his dyspnea. He was transferred to "Our Lady of Good Counsel" one month after his admission.

Results

From 1 January, 1965, to 1 December, 1967, 42 patients, nine women and 33 men, ranging in age from 17 to 90, with a median age of 65, underwent a total of 46 pleural biopsies. Of these, 41 were performed with the Cope needle and the remainder with the Abrams (Harefield) needle. Forty-one of the 42 patients had a pleural effusion at the time of the needle biopsy.

Complications

Out of 46 biopsies there was no mortality and no clinical morbidity. There were four asymptomatic pneumothoraces, none of which required chest tubes for resolution. These were small pneumothoraces, probably related to introduction via leakage of air through the biopsy needle. There were no tension pneumothoraces. Lung tissue was reported in one biopsy specimen, as well as pleura; and normal liver tissue was reported in two biopsies.

Malignant Effusions

As can be seen in Table 1, 15 patients who were subsequently found to have malignancy associated with effusion, underwent 17 needle biopsies. In seven of the 15 patients, a diagnosis was established. Thus in almost 50 per cent of the known malignant effusions the needle biopsy established the diagnosis. As can be seen in Table 2, two of the seven positive biopsies were obtained on the second attempt. Of the remaining eight patients who were subsequently demon-

TABLE 1

15 Patients with Final Diagnoses of Malignant Effusion

	Positive Pleural Bx	Non-Specific Fibrosis or Pleuritis	Inadeq. Spec.	Total No. of Bx
No. of Biopsies	7	6*	4†	17

*One of these six had biopsy repeated and malignancy diagnosed.

†One of these four had biopsy repeated and malignancy diagnosed.

TABLE 2

Malignancy Diagnosed by Re-Biopsy

	Diag. est. on 1st Bx	Diag. est. on 2nd Bx	Total
No.	5	2	7
%	71%	29%	

strated to have malignancies, none were re-biopsied, despite the fact that three of the eight were reported as having yielded inadequate specimens. One of these three patients subsequently had a thoracotomy which demonstrated metastases to the pleura. The remaining five had nonspecific pleurisy or fibrosis on the biopsy. Of the seven that did not have a diagnosis established by either needle or surgical biopsy, two were proven at autopsy to have had malignant pleural involvement and one was proven at autopsy not to have had pleural involvement. In conclusion, about 50 per cent of malignant effusions had a positive needle biopsy of the pleura, and approximately 30 per cent of the diagnoses were established on the second biopsy attempt.

Tuberculous Pleural Effusions

As can be seen in Table 3, there were only four patients in whom a diagnosis of tuberculous pleural effusion was established in this series of 42 patients, and of these four patients three were diagnosed solely on the basis of the biopsy. (Plus a positive skin test and an otherwise idiopathic pleural effusion.) Only one patient was found with an effusion, positive sputum cultures for tuberculosis, and a negative pleural biopsy. As before, on the patients with malignancy the biopsy was not repeated when the diagnosis of "nonspecific pleurisy or fibrosis" was recorded by the pathologist. Table 4 shows the results of pleural biopsy performed on 23 patients demonstrated to have neither cancer nor tuberculosis.

Non-diagnostic Biopsies

Inadequate biopsies comprised nine of the 46 specimens, or approximately 20 per cent. Eight of these did not have pleura submitted, just intercostal muscle and fat; the other inadequate specimen was hepatic tissue. Of the nine patients with inadequate biopsies, only one was re-biopsied and a diagnosis of carcinoma made. Of the remaining eight, three were subsequently proved to have carcinoma.

There were 23 biopsies on 20 patients in which a pathologic diagnosis of non-

TABLE 3

Four Patients with Final Diagnosis of Tuberculous Pleural Effusion

	Positive Pleural Bx.	Non-Spec. Pleuritis	Total
No. of Biopsies	3*	1†	4
%	75%	25%	

*A.F.B. cultures all were negative. Diagnosis established by biopsy.
†Culture positive for tuberculosis.

TABLE 4

Results of Pleural Biopsy on 23 Patients without Known TB or Cancer

Final Diagnosis	Non-Specific Fibrosis or Pleuritis	Normal Pleura	Inadequate Specimen	Total
Pulmonary embolus/infarct	2	1	2	5
C. H. F.	2	2	2	6
Empyema	3			3
Pneumonia	1			1
Miscellaneous or Undiagnosed	8	1	1	10

specific fibrosis or inflammation or pleuritis was made. Of these 20 patients only two were re-biopsied, and, as has been previously stated, one of these re-biopsies made the diagnosis of carcinoma. Out of the 20 patients with non-specific changes, six had malignancies and one had tuberculosis.

Summary of Studies

Forty-two patients underwent 46 needle biopsies of the pleura. Ten had positive diagnoses of carcinoma or tuberculosis established by needle biopsy, out of a total number of 19 patients, who subsequently were demonstrated to have either carcinoma or tuberculosis. This is a diagnostic "accuracy" of just greater than 50 per cent. In view of the high yield of re-biopsy (two of the three patients subjected to re-biopsy had a definite diagnosis of malignancy established), it is interesting to speculate what the yield might have been had all patients with a non-diagnostic initial biopsy been subjected to re-biopsy. None of the patients had any significant complications as a result of the biopsy. In our series, only one biopsy specimen was sent for tissue culture out of 46 biopsies performed.

TABLE 5

Summary of 42 Patients with 46 Biopsies

Final Diagnosis	Positive Biopsy	Non-Spec. Fibrosis or Pleuritis	Normal Pleura	Inadequate Specimen	Total
Malignancy	7	6		4	17
Tuberculosis	3	1			4
Pulmonary embolus/infarct		2	1	2	5
C. H. F.		2	2	2	6
Empyema		3			3
Pneumonia		1			1
Miscellaneous or Undiagnosed		8	1	1	10
TOTAL	10	23	4	9	46

Comment

Needle biopsy of the pleura has proved to be an effective and useful diagnostic procedure, as reported by many investigators.[2,20] Table 6 summarizes the diagnostic accuracy as reported by some of the many investigators who have published their experience. Virtually all of the reported series have stressed the fact that a histologic diagnosis of non-specific pleuritis, chronic inflammation, or fibrosis on the initial biopsy is, in fact, not a diagnosis at all. Virtually all authors have stressed the need for re-biopsy when a non-specific histologic picture has been obtained on the initial biopsy. Rao et al.[7] found nine of 32 cases with non-specific inflammation on initial needle biopsy to have either carcinoma or tuberculosis. Table 7 demonstrates the frequency with which the diagnosis was established by repeated biopsy in one series of 151 patients.[17]

Safety

The complications reported in the literature include pneumothorax, hemothorax, hepatic biopsy, lung biopsy, and intercostal neurectomy.[17,20,22] It has been the practice at Hennepin County General Hospital to perform pleural biopsy only in the presence of a demonstrated pleural effusion. However, Cope[15] specifically designed his biopsy needle to be used in the absence of pleural effusions. Three authors have reported their experience with this needle when used in the absence of effusion at the time of biopsy.[15,17,20] Niden et al. reported on 19 patients. Six had lung tissue in the biopsy without developing pneumothorax; three had small asymptomatic pneumothoraces; one patient with multiple subcutaneous hemorrhages but no demonstrable bleeding dyscrasia had a hemothorax. A positive diagnosis was established in seven of the ten patients with proven malignancy or tuberculosis.[20]

Levine and Cugell[17] reported 44 patients without effusion. In 90 per cent an adequate biopsy was obtained. One third had lung tissue in the biopsy; none had any complication as a result of this inadvertent lung biopsy. One patient who was already moribund from widespread carcinomatosis died five days after the biopsy. There seems to be no more morbidity or mortality associated with pleural biopsy in the absence of effusion than in the presence of effusion.

Case Selection

Several studies have been reported in which the diagnostic yield was reported as a percentage, based on the total number of patients or biopsies, and the number of positive diagnoses established by biopsy. This is misleading when one

TABLE 6

Needle Pleural Biopsy Results Selected from Review of the Literature

Author	Instrument	Final Dx Malig.	Needle Bx Malig.	%
Niden[20]	Cope	21	14	66%
Levine & Cugell[17]	Cope	28	21	75%
Samuels[8]	V-S	52	25	48%
Rao[7]	V-S	29	14	48%
Welsh[9]	V-S	14	10	70%
Leggat[13]	Abrams	20	12	60%
		Final Dx TBC	Needle Bx Dx TBC	
Niden[20]	Cope	6	4	66%
Levine & Cugell[17]	Cope	38	31	83%
Rao[7]	V-S	49	32	65%
Weiss[6]	V-S	58	47	80%

TABLE 7

Diagnosis Established by Repeated Biopsy*

No. Biopsy	No. of Diagnoses
1st	57
2nd	7
3rd	3
4th	3
TOTAL	70

*From Levine & Cugell[17].

attempts to ascertain the usefulness of any procedure, because prior case selection has such a great influence on diagnostic yield. Levine and Cugell[17] have shown, in a well-done study, the effect of careful prior case selection on the diagnostic yield. In their initial series, all patients with pleural effusions were biopsied, including those with obvious cardiac, renal and hepatic disease. They reported only 12 per cent positive biopsies. Their last 50 patients, selected with the criteria they developed, had a 68 per cent incidence of positive biopsies. Then for control purposes, they did 48 biopsies on 16 patients with pleural effusions, who did not meet their criteria, and none of these patients had positive biopsies, thus indicating that their criteria were probably not overly restrictive.

Their criteria:

"1. Any pleural effusion *not* occurring as a part of the clinical picture of congestive heart failure, cirrhosis, nephrosis, collagen disease, pneumonia, or trauma to the involved hemithorax;

2. Pleural fluid characteristic of an exudate (protein concentration above 2.5 gm.%) when a transudate was expected, e.g., congestive heart failure;

3. An area of unresolved pneumonitis impinging upon the chest wall—impingement considered likely if there was: (a) a history of localized pain, (b) physical findings of consolidation, pneumonitis, or localized swelling persisting for several weeks, and (c) roentgenologic evidence of contiguity with the chest wall."

Additional experience has shown[18] that patients with pulmonary embolus/infarct and empyema will have only non-specific pleural changes on repeated biopsies; and, in these cases, if a strong clinical case can be made, there is little reason to expect helpful information from pleural biopsy.

Bacteriology

As previously indicated, it has not been the practice at Hennepin County General Hospital to do bacteriologic cultures of pleural biopsy tissue specimens; however, Weichelhausen et al.[21] have reported positive tuberculosis cultures in six of 14 patients with tuberculous pleural effusions. In three of the six patients, the growth of M. tuberculosis was the only definitive evidence that these patients had tuberculosis, the pleural fluid cultures and pleural biopsy histology both being negative. Therefore Weichelhausen and colleagues recommend the immediate placement of the biopsy specimen in *Tween*® albumin medium, and the use of Dubos liquid medium for culture, because of its ability to support the growth of both M. tuberculosis and various fungal agents.

Contraindications

The only absolute contraindication to pleural biopsy would appear to be a bleeding tendency, although Cope[19] reported no untoward reactions in patients with prothrombin time as low as 40 per cent of normal. The absence of pleural effusion can be considered a relative contraindication at most; and the authors who have performed biopsies in the absence of effusion have reported minimal, if any, increase in morbidity and apparently do not consider the lack of effusion to be a contraindication. It would seem judicious to be cautious in the employment of this technique in the absence of effusion, and to have the biopsy performed by the most experienced physician available; but to judge from the experience of others, little difficulty is likely to be encountered.

Conclusions

Blunt-end, hook-needle biopsy of the parietal pleura is a safe, effective means of diagnosing disease involving the pleura. The diagnostic yield, with proper prior case selection, should approach 75 per cent in the diagnosis of tuberculous and malignant pleural effusions. Non-specific fibrosis or inflammation reported as a histologic diagnosis is not a clinical diagnosis; and, if the indications for biopsy were present for the initial attempt, the biopsy should be repeated to obtain a more definitive diagnosis, even in the absence of a recurrence of the pleural effusion. Our experience indicates a higher incidence of inadequate biopsies than several other series using the Cope needle. This probably reflects the large number of biopsies done by relatively inexperienced personnel, and perhaps inadequate prior familiarization with the proper technique. Bacteriologic cultures of pleural tissue represent an area of diagnostic effort that is not being utilized at present.

Acknowledgments

My thanks to Dr. Robert Strom, for reviewing and reinterpreting biopsy slides. Dr. Thomas Mulrooney, for his advice in the organization and preparation of this paper.

References may be secured from the Grand Round Editor.
See page 1034 for Protocol and Technique.

Visceral Larval Migrans Syndrome

This childhood syndrome consists of chronic eosinophilia and hepatomegaly associated in some cases with pulmonary involvement. Although Stewart (1933) first described two cases now recognized as the syndrome, Zuelzer and Apt (1949) described eight cases as comprising a distinct clinical entity with autopsy findings in one case. Children from one to four years of age are usually affected. At least 19 cases have been reported.

Clinical manifestations consist of chronic persistent hyperleukocytosis, moderate to severe eosinophilia, hyperglobulinemia, hepatic enlargement, and in some cases splenomegaly and pulmonary infiltration with symptoms of mild to moderate pneumonitis, often recurrent. Occasionally there is serious respiratory, central nervous system, or eye involvement.

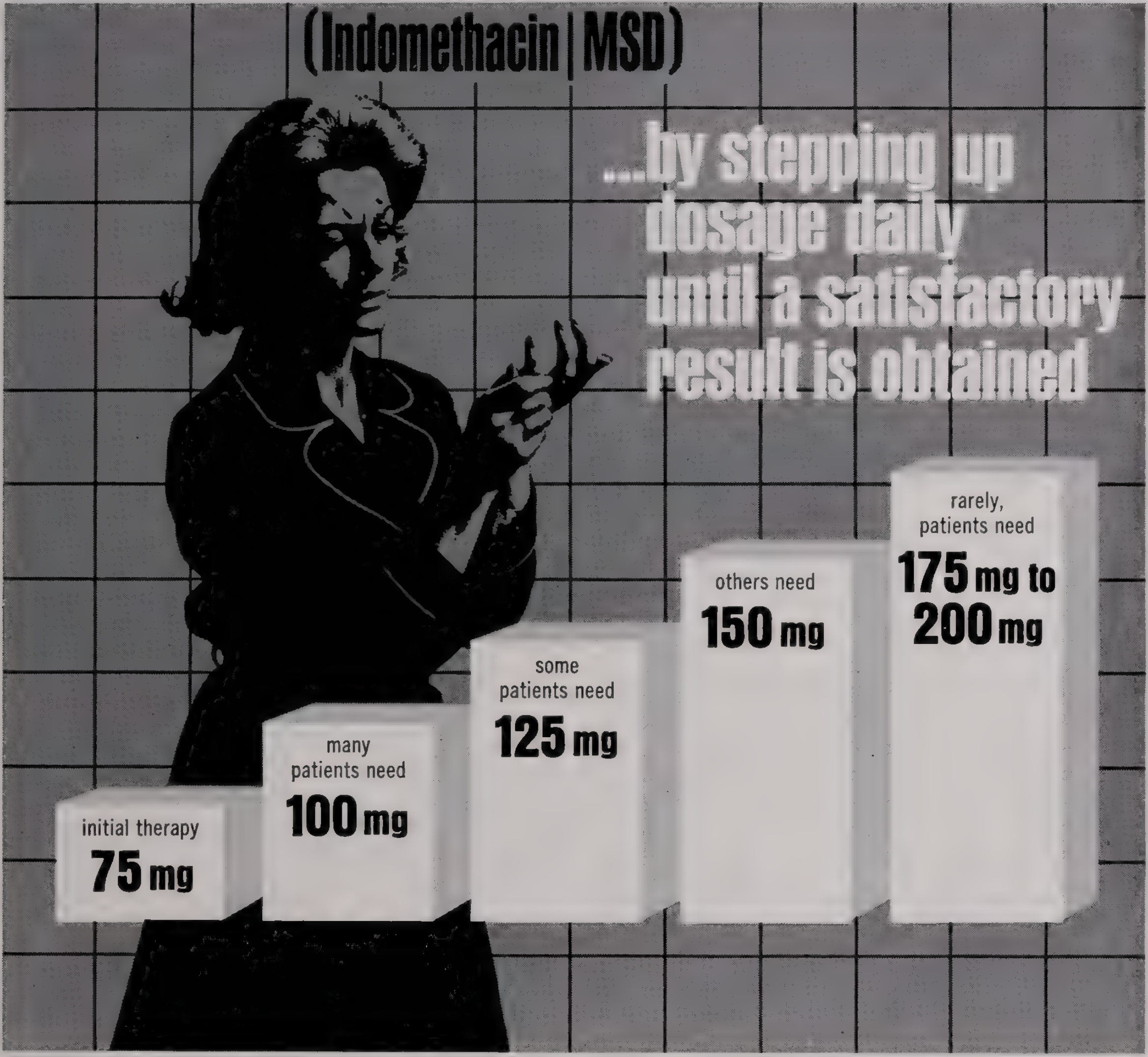
The etiologic agent in some cases has been proved to be liver invasion by nematode larvae. Biopsy has revealed eosinophilic infiltration and granulomatous lesions that contain larvae, shown by some investigators to be due to the ingestion of embryonated ova of dog or cat roundworms (*Toxocara canis* and *T. mystax*), as well as *Ascaris lumbricoides.* The course is self-limited but of long duration. A number of cases were asympatomatic, but the clinical findings in all cases persisted from one month to three years; nevertheless each child showed normal growth and development. Antihelminthic therapy is indicated, but it does not always alter the course.

Durham, Robert H.—Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York

Tact consists in knowing how far to go in going too far.—Cocteau

In selected cases of rheumatoid arthritis
with acute symptoms

Response to INDOCIN® is often improved...



Many patients with acute rheumatoid arthritis or acute episodes of chronic rheumatoid arthritis can be controlled by increasing the dosage 25 mg *per day* (to the allowable maximum) until the episode subsides; the dosage should then be reduced gradually to maintenance levels. Few require the maximum (175–200 mg).

In the event the patient develops adverse effects, dosage should be reduced to tolerated levels for 2 or 3 days and then gradually increased by 25 mg every few days as tolerated. G.I. effects may be minimized by giving INDOCIN with food, antacids, or immediately after meals.

Now in two strengths
25 mg and 50 mg

MSD 25
MSD 50

Actual Size

INDOCIN®
(Indomethacin|MSD)

IMPORTANT NOTE: INDOCIN (Indomethacin, MSD) cannot be considered a simple analgesic and should not be used in conditions other than those recommended under *Indications*. The drug should not be prescribed for children because safe conditions for use have not been established.

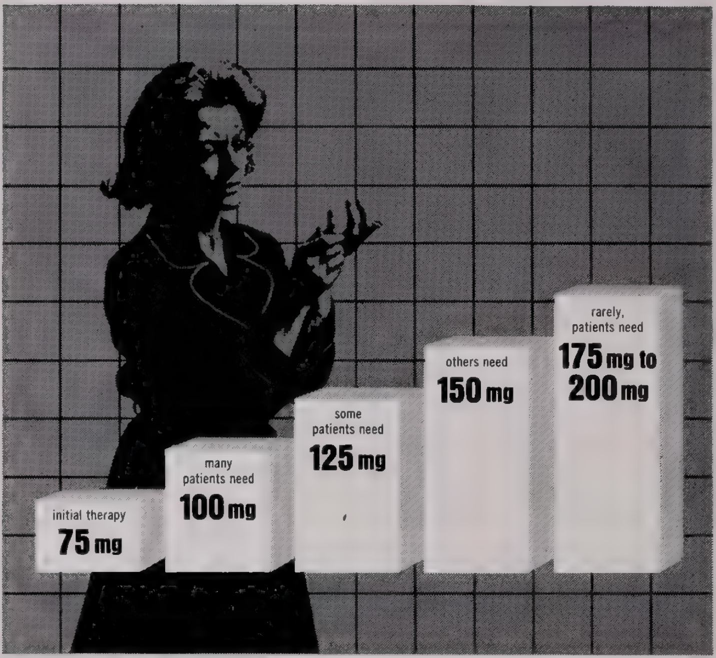
CONTRAINDICATED:

- in aspirin-sensitive asthmatics
- during pregnancy or lactation
- in children
- INDOCIN may mask the signs and symptoms of peptic ulcer and may cause ulceration or irritation of the G.I. tract. Therefore, do not give in active peptic ulcer, gastritis, regional enteritis, ulcerative colitis, and use with caution if there is a history of these disorders.

For additional prescribing information, please see following page.

In selected cases
of rheumatoid arthritis
with acute symptoms

Response to INDOCIN® (Indomethacin | MSD) is often improved by stepping up dosage daily until a satisfactory result is obtained



IMPORTANT NOTE: INDOCIN (Indomethacin, MSD) cannot be considered a simple analgesic and should not be used in conditions other than those recommended under Indications. The drug should not be prescribed for children because safe conditions for use have not been established.

Indications: For the symptomatic treatment of rheumatoid arthritis, rheumatoid (ankylosing) spondylitis, degenerative joint disease (osteoarthritis) of the hip, and gout.

Contraindications: INDOCIN may mask the signs and symptoms of peptic ulcer and may itself cause peptic ulceration or irritation of the G.I. tract. For these reasons it should not be given to patients with active peptic ulcer, gastritis, regional enteritis, or ulcerative colitis (use with caution if there is history of these disorders); aspirin-sensitive asthmatics. Safe use during pregnancy or during lactation has not been established. Should not be prescribed for children because safe conditions for use have not been established. In a few cases of severe juvenile rheumatoid arthritis receiving INDOCIN along with other drugs, severe reactions, including fatalities, have been reported.

Warnings: Patients who experience dizziness, lightheadedness, or feelings of detachment on INDOCIN should be cautioned against operating motor vehicles or machinery, climbing ladders, etc. Use cautiously in patients with psychiatric disturbances, epilepsy, or parkinsonism since it may aggravate these conditions.

Precautions: Use cautiously in patients with a history of peptic ulcer, gastritis, regional ileitis, or ulcerative colitis because of its potential for causing G.I. bleeding. May cause single or multiple ulceration of the esophagus, stomach, duodenum, or small intestine, and, in a few instances, severe bleeding and perforation with a few fatalities have been reported. May potentiate the ulcerogenic effect of steroids, salicylates, or phenylbutazone. Gastrointestinal bleeding with no obvious ulcer formation has also been noted; the drug should be discontinued if G.I. bleeding occurs. As a result of obvious or occult G.I. bleeding, some patients may manifest anemia, and for this reason periodic hemoglobin determinations are recommended. G.I. effects may be minimized by giving the drug with food or with antacids or immediately after meals. In common with other drugs that have anti-inflammatory, analgesic, and antipyretic properties, indomethacin may mask the signs and symptoms of infection; avoid undue delay in initiating appropriate treatment of the infection; use cautiously in patients with existing, but controlled, infections. As with any new drug, patients should be followed carefully to detect unusual manifestations of drug sensitivity.

Adverse Reactions: Starting therapy with low doses, with gradual increases when necessary, will minimize adverse reactions. *Central Nervous System:* Most commonly, headache (usually more severe in morning), dizziness, and lightheadedness; infrequently observed reactions include mental confusion, drowsiness, convulsions, coma, depression, and other psychic disturbances, such as depersonalization; CNS effects are often transient and frequently disappear with continued treatment or reduced dosage. The severity of these effects may occasionally require cessation of therapy. *Gastrointestinal:* Most commonly, nausea, anorexia, vomiting, epigastric distress, abdominal pain, and diarrhea; others that may develop are ulceration, single or multiple, of esophagus, stomach, duodenum, or small intestine, including perforation and hemorrhage with a few fatalities having been reported; G.I. bleeding without obvious ulcer formation, increased abdominal pain in patients with preexisting ulcerative colitis; less commonly, stomatitis; gastritis; bleeding from the sigmoid colon, occult in type or from a diverticulum, and perforation of preexisting sigmoid lesions (diverticulum, carcinoma); G.I. reactions not known definitely to be attributable to indomethacin include development of ulcerative colitis and of regional ileitis. *Hepatic:* Rarely, jaundice and hepatitis. *Cardiovascular-Renal:* Infrequently, edema, elevation of blood pressure, and hematuria. *Dermatologic-Hypersensitivity:* Infrequently, pruritus, urticaria, angioneurotic edema, angiitis, skin rashes, loss of hair, and acute respiratory distress including sudden dyspnea and asthma. *Hematologic:* Infrequently, leukopenia, purpura, and thrombocytopenia; rarely, agranulocytosis and bone marrow depression have been reported, but a definite relationship to the drug has not been established; since some patients may manifest anemia secondary to obvious or occult G.I. bleeding, periodic hemoglobin determinations are recommended. *Eye-Ear:* Infrequently, tinnitus, blurred vision, hearing disturbance, and orbital and periorbital pain. *Miscellaneous:* Rarely, vaginal bleeding, hyperglycemia, and glycosuria.

Supplied: Capsules containing 25 mg indomethacin each, in bottles of 100 and 1000; capsules containing 50 mg indomethacin each, in bottles of 100.

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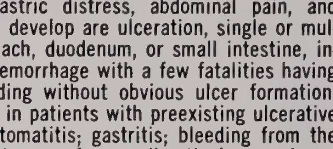

MERCK SHARP & DOHME Division of Merck & Co Inc West Point Pa 19486

WHERE TODAY'S THEORY IS TOMORROW'S THERAPY

Diagnostic Problem

Subinguinal Varix*

THE SUBINGUINAL VARIX sometimes presents a problem of diagnosis and treatment because it is easily misdiagnosed as a femoral hernia from the similarity in location, size, and globular appearance. Other protruding masses in the groin must be included in the differential diagnosis of this venous tumor. A correct diagnosis is essential, since otherwise the preparation will not be adequate for operation on varicose veins.

Many patients with this globular varix in the groin have been examined during the past two decades in the Section of Peripheral Vein Surgery of the Mayo Clinic. Quite often the initial diagnosis made by a resident or consultant was femoral hernia.

Anatomy

The anatomic relationships in the femoral (Scarpa's) triangle must be kept in mind when examining protruding masses in the groin. This triangle is bounded superiorly by the inguinal ligament, laterally by the sartorius muscle, and medially by the adductor longus muscle. Important structures within it are the femoral canal, femoral vein and artery, and femoral nerve, all invested by the femoral sheath. The great saphenous vein originates from the femoral vein, emerges through the fossa ovalis just below the inguinal ligament, and courses diagonally downward and medially over the inner thigh and leg. The femoral canal terminates in the fossa ovalis; thus a large femoral hernia protrudes through this aperture and appears also as a bulging mass in the same location as a subinguinal varix. The triangle also contains numerous subinguinal lymph nodes which are usually small and insignificant.

Differential Diagnosis

The subinguinal varix must be differentiated from other protruding masses in the groin, the most common of which is femoral hernia. This varix is a peculiar, saccular dilatation of a very short proximal segment of the great saphenous vein, just distal to its origin from the femoral vein but superficial to the fossa ovalis and femoral sheath. This proximal portion of the saphenous vein is not only poorly supported by surrounding tissues but also exposed to high venous pressures caused by increased intra-abdominal pressure during coughing, straining, or lifting.

A femoral hernia protrudes from the intra-abdominal space downward into and through the femoral canal and then courses laterally and outward along the path of least resistance until it protrudes through the fossa ovalis along with the great saphenous vein. The sac of the femoral hernia may be small and is often preceded by a large amount of extraperitoneal fat. The protruding mass may thus appear as an elongated, elastic swelling of considerable size. The sac often contains an omental tag, and the hernia is seldom more than partially reducible into the femoral canal. Femoral hernia, which is always acquired (in contrast to inguinal hernia), occurs more frequently in females than in males (three to four times more commonly), probably because of the greater proportional width of the pelvis and the greater size of the femoral ring. The small neck of a large femoral hernia protrudes *below* the inguinal ligament through the fossa ovalis, whereas the neck of an inguinal hernia protrudes *above* the ligament.

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*Read at the meeting of the Southern Minnesota Medical Association, Owatonna, September 20, 1968.

Other protruding masses in the groin, though less likely to be confused with the saphenous varix but still included in the differential diagnosis, are a solitary enlarged lymph node, a lipoma, a hydrocele of the spermatic cord or of the canal of Nuck, and an undescended testicle. An enlarged lymph node is firm and irreducible, tender when inflamed, and usually associated with a recent infection of the regional skin or subcutaneous tissues. A lipoma is soft, nontender, and freely movable on palpation. A hydrocele will transilluminate, and its location is typically above and medial to the pubic spine, along the course of the spermatic cord in the male, or the canal of Nuck in the female. An undescended testicle has a similar location in the male.

Diagnosis

The diagnosis of a subinguinal varix is based on (1) its location—just below and superficial to the fossa ovalis; (2) its reducibility—prompt on finger pressure or on change from standing to reclining posture; (3) its association with other varicosities in the lower limb; and (4) its transmission of a venous impulse along the course of the great saphenous vein—a characteristic and most helpful finding.

The transmission of the venous impulse is the most significant diagnostic finding. This test is performed by quickly compressing the varix in the groin with the fingers of one hand and palpating the transmitted impulse along the course of the great saphenous vein by the fingers of the other hand, just above the inner aspect of the knee. The venous impulse can likewise be transmitted upward into the subinguinal varix by quickly compressing the saphenous vein below. This particular test *conclusively* differentiates a saphenous varix from a femoral hernia. The cough impulse occurs with either a varix or a hernia and is therefore not a reliable test in the differential diagnosis. The transmission of a venous impulse does *not* occur with other protruding masses in the groin. A case is illustrated in the Figure.

Observations in 10 Cases

Many patients who were operated on for varicose veins during the past two decades had groin lesions varying from a minimal local dilatation to a round mass with a diameter of 5 or 6 cm. Ten patients were selected for review because their groin lesions had a confusing resemblance to femoral hernia. In

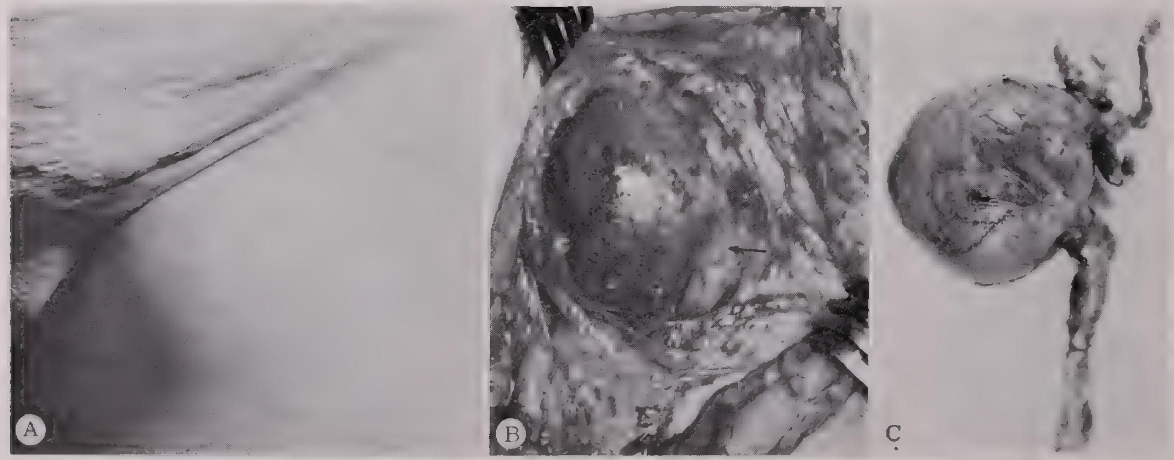

Figure: Subinguinal varix in left groin. *A*, Clinical appearance. *B*, Exposure of varix in groin incision. Arrow indicates great saphenous vein. *C*, Surgical specimen showing round varix 4 cm in diameter.

all, the onset had been insidious and without acute pain. The clinical diagnosis on initial examination was femoral hernia (incorrect) in five cases and saphenous varix (correct) in five. The globular varix was situated in the right groin in five patients and in the left groin in four, and one patient had a round mass in each groin. Eight patients were women and two were men. Their ages ranged from 30 to 74 years. All had associated incompetency of the great saphenous vein in one or both legs.

Summary

1. The subinguinal varix is easily mistaken for a femoral hernia because of similarity in location, size, and appearance.
2. It is promptly reduced by finger pressure or by change from a standing to a reclining posture, and it is usually associated with other varicosities in the leg.
3. Transmission of a venous impulse is characteristic and confirms the diagnosis of subinguinal varix.
4. The treatment is surgical removal of the subinguinal varix and of the incompetent great saphenous system from the foot to the saphenofemoral juncture.

Karl A. Lofgren, M.D.*
Rochester, Minnesota

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*Mayo Clinic and Mayo Foundation: Section of Peripheral Vein Surgery.

Shakespeare: Diseases

Epilepsy

Among Shakespeare's repertoire of dramatic stage devices, epilepsy furnishes two sensational examples: one in *Othello,* another in *Julius Caesar.*

Listening in on Iago's and Cassio's dialogue we hear:

Iago: How now, Cassio!
Cassio: What's the matter?
Iago: My lord is fallen into an epilepsy:
This is his second fit; he had one yesterday.
Cassio: Rub him about the temples.
Iago: No, forbear;
The lethargy must have his quiet course:
If not, he foams at mouth, and by-and-by
Breaks out to savage madness. Look, he stirs:
Do you withdraw yourself a little while;
He will recover straight.*

Joining Brutus, Cassius, and Casca in a public square in Rome we overhear:

Cassius: What, did Caesar swoon?
Casca: He fell down in the market-place, and foamed at mouth, and was speechless.
Brutus: 'Tis very like: he hath the falling-sickness.
Casca: When he came to himself again he said, if he had done or said anything amiss, he desired their Worships to think it was his infirmity.†

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*Othello: IV, 1
†Julius Caesar: I, 2

Convalescing . . . but still a long way to go. Anxiety can make it even longer.

Convalescence following medical or surgical procedures may be almost endless to an anxious patient. And, indeed, anxiety with some patients actually retards progress—for example, by inducing insomnia and reducing cooperation.

As physicians have found during nearly 15 years of widespread use, Equanil may be a beneficial part of aftercare. It helps relieve anxiety and tension, thus often aiding your primary therapy.

Indications: For use in management of anxiety and tension occurring alone or as accompanying symptom complex to medical and surgical disorders and procedures. Though not a hypnotic, fosters normal sleep through antianxiety and related muscle-relaxant properties.

Contraindications: History of sensitivity to meprobamate.

Important Precautions: Carefully supervise dose and amounts prescribed, especially for patients prone to overdose themselves. Excessive prolonged use has been reported to result in dependence or habituation in susceptible persons, as alcoholics, ex-addicts, and other severe psychoneurotics. After prolonged excessive dosage, reduce dosage gradually to avoid possibly severe withdrawal reactions. Abrupt discontinuance of excessive doses has sometimes resulted in epileptiform seizures.

Warn patients of possible reduced alcohol tolerance, with resultant slowing of reaction time and impairment of judgment and coordination.

Reduce dose if drowsiness, ataxia or visual disturbance occurs; if persistent, patients should not operate vehicles or dangerous machinery.

Side Effects include drowsiness, usually transient; if persistent and associated with ataxia, usually responds to dose reduction; occasionally concomitant CNS stimulants (amphetamine, mephentermine sulfate) are desirable. Allergic or idiosyncratic reactions are rare, but such reactions, sometimes severe, can develop in patients receiving only 1 to 4 doses who have had no previous contact with meprobamate. Previous history of allergy may or may not be related to incidence of reactions. Mild reactions are characterized by itchy urticarial or erythematous maculopapular rash, generalized or confined to groin. Acute nonthrombocytopenic purpura with cutaneous petechiae, ecchymoses, peripheral edema and fever have been reported. One fatal case of bullous dermatitis following intermittent use of meprobamate with prednisolone has been reported. If allergic reaction occurs, meprobamate should be stopped and not reinstituted. Severe reactions, observed very rarely, include angioneurotic edema, bronchial spasms, fever, fainting spells, hypotensive crises (1 fatal case), anaphylaxis, stomatitis and proctitis (1 case) and hyperthermia. Treat symptomatically as with epinephrine, antihistamine and possibly hydrocortisone. Aplastic anemia (1 fatal case), thrombocytopenic purpura, agranulocytosis and hemolytic anemia have occurred rarely, almost always in presence of known toxic agents. A few cases of leukopenia, usually transient, have been reported on continuous administration.

Meprobamate may sometimes precipitate grand mal attacks in patients susceptible to both grand and petit mal. Extremely large doses can produce rhythmic fast activity in the cortical pattern. Impairment of accommodation and visual acuity has been reported rarely. After excessive dosage for weeks or months, withdraw gradually (1 or 2 weeks) to avoid recurrence of pretreatment symptoms (insomnia, severe anxiety, anorexia). Abrupt discontinuance of excessive doses has sometimes resulted in vomiting, ataxia, tremors, muscle twitching and epileptiform seizures. Prescribe very cautiously and in small amounts for patients with suicidal tendencies. Suicidal attempts have resulted in coma, shock, vasomotor and respiratory collapse and anuria. Excessive doses have resulted in prompt sleep; reduction of blood pressure, pulse and respiratory rates to basal levels; and occasionally hyperventilation. Treat with immediate gastric lavage and appropriate symptomatic therapy. (CNS stimulants and pressor amines as indicated.) Doses above 2400 mg./day are not recommended.

Composition: Tablets, 200 mg. and 400 mg. meprobamate. Coated Tablets, WYSEALS® EQUANIL (meprobamate) 400 mg. (All tablets also available in REDIPAK® [strip pack], Wyeth.) Continuous-Release Capsules, EQUANIL L-A (meprobamate) 400 mg.

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Abstracts, Briefs and Commentaries

EMPYEMA OF THE THORAX IN ADULTS

Thoracic empyema has become an uncommon disease in adults tending to occur in chronically ill individuals. In this series of 105 cases, underlying pneumonia was the cause of the empyema in more than half the cases. Empyema resulted from prior thoracic surgery in almost one quarter of all cases. Staphylococcus aureus and gram-negative bacilli were the most commonly found organisms. Successful therapy is founded on correct choice and adequate dose of antibiotics, prompt institution of adequate drainage and recognition and treatment of underlying factors. Chronic cases of empyema were treated by decortication, pulmonary resection and thoracoplasty. Mortality was less than five percent from the empyema.

Theodore A. Peterson, M.D.
Minneapolis, Minnesota

Snider, G. L., and Saleh, S. S.: Empyema of the Thorax in Adults: Review of 105 Cases. Dis Chest 54: 5:410, 1968.

TREATMENT OF HYPERTENSION

A follow-up study of 97 hypertensive patients with group 3 hypertension (or retinopathy) and 64 patients with malignant (group 4) hypertension clearly demonstrated that medical treatment improves the prognosis, although the mortality rate remained disappointingly high. The five-year survival rate was 37.5% for patients with group 3 retinopathy and 28.6% for patients with malignant hypertension. Inadequate control of blood pressure, cessation of therapy, short duration of hypertension, and significant azotemia were associated with worse-than-average mortality rates. Effective treatment not only prolonged life but led to the regression of retinal hemorrhages, exudates and papilledema; but control of the hypertension did not seem to influence favorably those complications that are due to atherosclerosis, especially cerebrovascular accident. More than 10% of the survivors suffered cerebral vascular accidents, and this complication was the leading cause of death in this series. The marked relationship found between the degree of control of hypertension and longer survival suggests that more effective and better tolerated drugs will further improve the prognosis in severe hypertension.

Courtesy of References and Reviews
Journal of the American Medical Association

Farmer, R., Gifford, R., and Hines, E.: Arch Intern Med 112:118, 1963.

PERFORATION OF RIGHT VENTRICULAR WALL BY THE ENDOCARDIAL PACING CATHETER

Four clinically documented cases of the right ventricular wall perforation, due to a hard-tipped intravenous pacemaker catheter are presented. One patient expired. The cause of death was pericardial tamponade caused by the hemorrhage into the pericardium through the perforation. The other three cases were found at the time of thoracotomy but resulted in no detectable complication. Use of soft-tipped pacing catheters, along with careful manipulation under fluoroscopic guidance, should lessen the chance of myocardial perforation in cases of intravenous pacemaker implantation. The cases of perforation of the myocardium were all in patients in whom a pacing catheter had been used.

Theodore A. Peterson, M.D.
Minneapolis, Minnesota

Hirose, T., Vera, C. A., Bailey, C. P., and Edberg, S. H.: Perforation of Right Ventricular Wall by the Endocardial Pacing Catheter. Dis Chest 54:6-510, 1968.

GASTRIC LYMPHOMA

Two pathologists made a retrospective survey of 71 patients with gastric lymphoma. At the time of diagnosis 65 patients had primary gastric tumors and six cases were associated with diffuse disease. Most patients had less than six months of symptoms. The five-year and ten-year survival rates for primary lesions were 59 and 28 percent. The best prognosis occurred with small, superficial lesions confined to the stomach. In long-term survivals, lymphoma of the stomach is not necessarily a manifestation of systemic disease.

Richard L. Reece, M.D.
Minneapolis, Minnesota

Joseph, J. I., and Lattes, R.: Gastric Lymphoma. Amer J Clin Path 45:653, 1966.

PREVENTION OF RECURRENT PULMONARY EMBOLI WITH ANTICOAGULANTS

This resume of treatment of 704 patients with pulmonary thrombo-embolism leads to the conclusion that oral anticoagulants are beneficial. In treated patients, if the Quick one-stage prothrombin time was more than 1.6 times control, the rate of recurrent pulmonary embolism was reduced to 2 percent. A higher incidence (10.4 percent) was reported in patients for whom therapy was inadequate (prothrombin time less than 1.6 times control value). No mention was made of ligation or plication of vena cava in this large series of patients.

Theodore A. Peterson, M.D.
Minneapolis, Minnesota

Lang, K. F., and Schatz, I. J.: Prevention of Recurrent Pulmonary Emboli with Anticoagulants. Dis Chest 54: 5:416, 1968.

Derivatively Speaking

Vaccine—from Latin *vacca* (a cow)

MALIGNANT MELANOMA OF THE PENIS

The authors were able to collect only 23 published reports on melanoma of the penis with a world-wide distribution. Wattenberg collected only eleven reported cases in 1944. Ten cases ranged from 48 to 78 years of age. Nine occurred on the glans and one on the prepuce; seven had secondary deposits when first seen. Four more were reported by MacDermott and Kennedy in 1955. Abeshouse and Goldstein collected 18 cases in 1962. Buddington Kitckham and Smith in 1963 found only one melanoma in 104 consecutive primary malignancies of this organ. Gupta and Grabstald in 1965, in no less than 1200 malignant melanomas, found only one involving the penis.

Case Report

A 44-year-old male was admitted to Westminster Hospital, London, in 1966. Twelve months previously he had noticed a black spot on the under side of his glans penis. One month before admission he had noted superficial ulceration and slight bleeding. He was unmarried, had been circumcised in infancy and had no history of venereal disease. Examination of the glans revealed grey-black spots, flat, with the same consistency as the surrounding area. The ulcerated point was near the urethral orifice 0.5 cm. in diameter in a pigmented zone.

Physical examination was negative; biopsy consisting of a partial amputation revealed a malignant melanoma. Amputation proximal to the glans proved to be well below the growth.

Treatment—Lugols solution 10 minims was given three times daily for three days. A vessel on the right side of the shaft near its base was cannulated. Lipiodol with ^{131}I was injected under pressure to extravasate around the lymphatics. Radiographs showed that nodes in the left groin had filled and that there was some extravasation deep to the skin covering the penis. No vessel being available on the right side of the penis a right pedal vessel was cannulated and additional ^{131}I in lipiodol was injected.

Lymphograms showed good filling of the lymph nodes in the inguinal, iliac and lower para-aortic nodes on the right and iliac and lower para-aortic nodes on the left. The thyroid showed no uptake.

Progress: Twenty-one months from the date of operation the patient is well, free from clinical recurrence with normal chest x-rays. There has been moderate edema of the right leg and two episodes of erysipelas-like infection.

Discussion

Melanoma of the penis is rare and the effects of various types of treatment are scant, with only two long-time survivals. Invasion of inguinal lymph nodes is grave. Radiotherapy is of doubtful value. Management of regional nodes can be expectant only, or comprise active therapy by bilateral block dissection or by endolymphatic therapy using radioactive material.

The endolymphatic therapy using radioactive gold produces destruction of lymphatic vessels and nodes not suitable for surgical ablation. Since the development of ^{131}I lipiodol the same result is accomplished with less extravasation.

Stanley R. Maxeiner, Sr., M.D.
Minneapolis, Minnesota

Ellis, Harold and White, W. F., Westminster Hospital, London: Malignant Melanoma of the Penis: Endolymphatic Therapy with ^{131}I Lipiodol.

It is better to wear out one's shoes than one's sheets.—Genoese proverb

Special Article

Controlled Oxygen Administration in Respiratory Failure

DAVID E. DINES, M.D.*
JUI-SUNG HUNG, M.D.†
WILLIAM F. REILLY, JR., M.D.†
RICHARD A. WILLSON, M.D.†
Rochester, Minnesota

THE RELENTLESS RISE in the incidence of chronic obstructive pulmonary disease has demanded that physicians become familiar with the basic management of acute respiratory failure. It is well known that controlled oxygen in respiratory failure should be aimed at correcting the hypoxia to a safe level without enhancing the respiratory acidosis.

Barach[1] introduced the concept of regulated oxygen therapy by the use of low flow rates of oxygen in 1938, but the importance of the concept of correcting the hypoxia was not appreciated until Campbell[2,3] in 1960 and Massaro and associates[4] and Kory and co-workers[5] in 1962 made comparative evaluations of oxygen therapy in respiratory failure.

In addition to the necessity for low concentration of oxygen, the manner in which it is delivered is exceedingly important. In 1954 Cohn and associates[6] recommended the intermittent administration of oxygen, with short periods of air breathing, for patients with acute carbon dioxide retention. Campbell[7] pointed out that intermittent administration of oxygen may produce more deleterious effects, as the depressant action persists for some time after the oxygen has been withdrawn and may result in more severe hypoxia than existed before the oxygen was administered. This occurs because a decrease in the concentration of oxygen in the inspired air results in an immediate change in arterial oxygen concentration; the change is immediate because of the small stores of oxygen in the body.

Kory and associates[5] and Barach[8] found that adequate inspired concentrations of oxygen could be achieved with nasal cannula. Conversely, Longobardi and co-workers[9] concluded that only insufflation of oxygen into the oropharynx by catheter gave reliable concentrations of oxygen. Cherniack and Hakimpour[10] have advocated low flow rates through nasal cannula at 2 to 3 liters/min, and they have demonstrated correction of arterial hypoxia with 2 to 3 liters/min and no further hypercapnia.‡ Campbell and Gebbie[11] stated the belief that the level of inspired oxygen concentration is critical in respiratory failure because of the possibility of precipitating further retention of carbon dioxide and have recommended the "Ventimask," a plastic disposable mask that operates on the Venturi principle. Schiff and Massaro[12] have found this type of mask preferable to the nasal catheter for oxygen administration. Mithoefer and associates[13] found that the Ventimask at 24, 28, and 35% frequently failed to correct hypoxia to a safe level, and 24% of the patients receiving 35% oxygen had oxygen tensions below 50 mm Hg.

The necessity of lessening hypoxemia during acute respiratory failure in patients with chronic obstructive pulmonary disease is well accepted. Oxygen therapy in an uncontrolled fashion may lead to deterioration of ventilation, increased acidosis, and occasionally coma.

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*Mayo Clinic and Mayo Foundation: Section of Medicine.
†Mayo Graduate School of Medicine (University of Minnesota): Residents in Medicine.
‡See Test Your Word Score Page 933.

Controlled, low concentrations of inspired oxygen have been devised by Campbell and Gebbie,[11] utilizing a plastic disposable mask (Figure) specifically designed to deliver 24, 28, or 35% oxygen. Four liters/min are delivered with the 24 and 28% Ventimask and 8 liters/min with the 35% Ventimask. The masks are perforated to provide known concentrations of 24, 28, or 35% oxygen.

Four patients with chronic obstructive pulmonary disease are presented to show what happens to the arterial oxygen tension (Pa_{O_2}), arterial carbon dioxide tension (Pa_{CO_2}), and pH, when oxygen is administered to patients with pulmonary insufficiency. A comparison also has been made between oxygen administered by Ventimask and oxygen administered by nasal cannula in two of the patients with pulmonary insufficiency.

Report of Cases

Case 1

A 68-year-old mechanic with known chronic obstructive pulmonary disease was admitted to the hospital on December 5, 1967, because of increased shortness of breath.

On examination he was cyanotic at rest and tachypneic (respiration rate 28/min). There was expiratory slowing of grade 3, and the pulmonary closure sound was accentuated.

The hemoglobin value was 15 gm/100 ml of serum, and the hematocrit reading was 56%. The electrocardiogram showed a prominent P wave in lead II, right axis deviation, and a right ventricular conduction delay. A chest roentgenogram showed prominent pulmonary artery segments bilaterally and hyperlucency of the lungs at both bases. Pulmonary function tests had not been done since 1960; at that time these showed an obstructive pattern with the ratio of residual volume to total capacity elevated to 73%, a maximal breathing capacity of 35 liters/min, expiratory slowing of grade 4, elevation of the nitrogen washout to 6.0%, and a resting arterial oxygen saturation of 86%.

Arterial blood gas values are listed in the Table.

The patient was treated with low-flow oxygen at 2 liters/min, intermittent positive pressure, bronchodilators, sodium restriction, expectorants, and digitalis. Diuresis resulted in loss of 17 pounds in two weeks.

Comment

This is an example of a patient with chronic obstructive pulmonary disease, emphysema, and chronic bronchitis, who was hypoxic at rest (arterial oxygen tension, 44 mm Hg). He was given oxygen by nasal cannula at 2 liters/min, and the arterial oxygen tension increased to 60 mm Hg, with only a slight rise in the arterial carbon dioxide tension to 63 mm Hg. The arterial oxygen tension of 60 mm Hg was in a safe range, which shows the effectiveness of controlled, low-flow oxygen at 2 liters/min by nasal cannula.

Next, the 24% Ventimask was utilized, and the arterial oxygen tension was increased to 55 mm Hg, a safe level but not as high as achieved with nasal cannula at 2 liters/min.

The 28% Ventimask increased the arterial oxygen tension to 96 mm Hg, but with a dangerous rise in the arterial carbon dioxide tension to 80 mm Hg and a drop in pH to 7.27.

Case 2

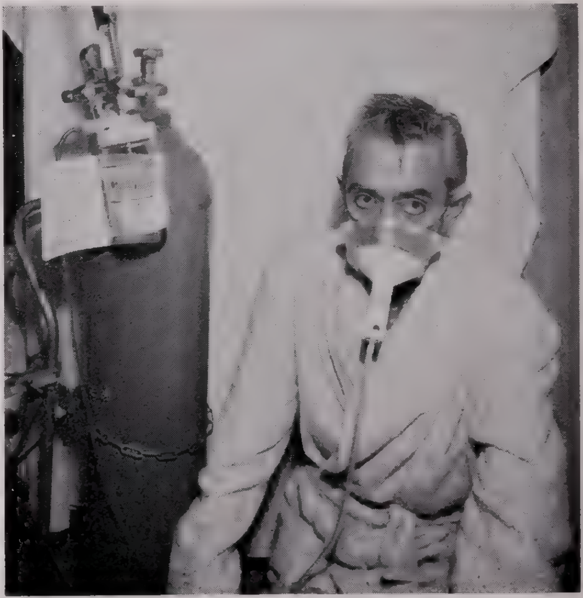
A 53-year-old cattle inspector was admitted to the hospital on November 13, 1967, with productive cough, shortness of breath, orthopnea, and ankle edema.

On admission he was cyanotic, tachypneic, and orthopneic, with hyperresonance to percussion, rales at both bases, scattered rhonchi and wheezes, and expiratory slowing of grade 3.

The hemoglobin value was 16 gm/100 ml of serum, and the hematocrit reading was 59%. The electrocardiogram revealed right axis deviation with enlargement of the right atrium and right ventricle. A chest roentgenogram showed prominent pulmonary artery segments and vascular congestion. Pulmonary function, performed after diuresis, revealed an obstructive pattern with a maximal breathing capacity of 30 liters/min, a maximal midexpiratory flow rate of 0.4 liters/sec, a nitrogen washout of 6.9%, and an arterial oxygen desaturation to 79% at rest. A carbon monoxide diffusing capacity was 5 ml/min/mm Hg (normal 22).

Arterial blood gas values are listed in the Table.

The patient was treated with low-flow oxygen using the 28% Ventimask, intermittent positive pressure, bron-



Figure

Example of disposable plastic mask used in delivery of controlled, low concentrations of inspired oxygen.

chodilators, expectorants, and diuretics; and he was slowly digitalized. Diuresis resulted in a loss of 30 pounds while in the hospital. Two pints of blood were removed on successive days to decrease the hematocrit level to 54%.

Comment

The second patient has severe chronic obstructive pulmonary disease with chronic bronchitis, emphysema, cor pulmonale, congestive failure, profound hypoxia, and hypercapnia. The arterial oxygen tension was 31 mm Hg at room air. On two successive days, oxygen by nasal cannula at 2 liters/min increased the arterial oxygen tension to only 37 and 39 mm Hg, respectively. The 24% Ventimask increased the arterial oxygen tension to 47 mm Hg, but still the level was not in a safe range. The 28% Ventimask increased the arterial oxygen tension to 62 mm Hg without further hypercapnia. Because oxygen saturation of 90% was achieved with the 28% Ventimask, there was no consideration of using the 35% Ventimask, which would only lead to further hypercapnia to the level of narcosis.

Case 3

A 58-year-old white man was admitted because of a 10-year history of shortness of breath.

On examination he was plethoric and cyanotic and had expiratory slowing of grade 4.

The hemoglobin value was 17.8 gm/100 ml of serum, and the hematocrit value was 59%. Pulmonary function showed an obstructive pattern with a maximal breathing capacity of 68 liters/min (estimated normal for this patient, 120), a maximal midexpiratory flow rate of 0.8 liters/sec, and a nitrogen washout of 4.2%. The arterial oxygen saturation was 95% at rest. A chest roentgenogram was suggestive of hyperaeration, with prominent pulmonary artery segments. The electrocardiogram showed only a right axis deviation.

Values for arterial blood gas tension are listed in the Table.

Comment

Case 3 is included to show how oxygen saturation from ear oximetry* may not give the true picture. Patient 3 had chronic obstructive pulmonary disease with emphysema and chronic bronchitis, mild secondary polycythemia, and a low arterial oxygen tension (65 mm Hg). This case illustrates that hypoxemia in chronic obstructive pulmonary disease may occur with or without hypercapnia. Therapy with low-flow oxygen using nasal cannula at 2 liters/min increased the arterial oxygen tension to 84 mm Hg without a dangerous rise in the arterial carbon dioxide tension. The 24% Ventimask would give the same results. Oxygen was administered by nasal cannula at 2 liters/min to show that low-flow oxygen can be given safely without affecting the arterial carbon dioxide tension.

Case 4

A 55-year-old man was admitted to the hospital on February 28, 1968, profoundly dyspneic, with a known diagnosis of chronic obstructive pulmonary disease, chronic bronchitis, bronchiectasis, and cor pulmonale. He was in right ventricular failure; he had bronchopneumonia with fever, cough, and purulent sputum; he was hypoxic, hypercapneic, and polycythemic. A chest roentgenogram showed honeycombing in both bases, pulmonary vascular congestion, bullous changes in both upper lobes, and prominent pulmonary artery segments indicative of cor pulmonale. Pulmonary function, performed at a time when he was not in failure, showed an obstructive pattern with a high nitrogen washout index of 11.9% (normal less than 2.5) and arterial oxygen desaturation.

On admission, he had an arterial oxygen tension of 35 mm Hg and an arterial carbon dioxide tension of 56 mm Hg with an arterial pH of 7.26 (Table). He was given low-flow oxygen by nasal cannula at 2 liters/min, along with intermittent positive-pressure breathing, aminophylline, expectorants, and broad-spectrum antibiotics. A phlebotomy was performed, and he was given 1.0 mg of digoxin. Seven hours later, the arterial oxygen tension was 59 mm Hg, but the arterial carbon dioxide tension had risen to 92 mm Hg and the pH had dropped to 7.14. Assisted ventilation became necessary with an oral tracheal tube and a Bird valve. Twenty-four hours later the arterial oxygen tension was 97 mm Hg, the arterial carbon dioxide tension 57 mm Hg, and the pH 7.30 (Table).

Comment

This is an example of a patient with chronic obstructive pulmonary disease, chronic bronchitis, bronchiectasis, cor pulmonale, and right ventricular failure, in whom low-flow oxygen by nasal cannula was not successful because of the severe secretion problem, pneumonitis, and superimposed pulmonary congestion. An oral tracheal tube and assisted ventilation became necessary. It does show the importance of adequate monitoring with arterial blood gases, and how mandatory it is to intubate and assist ventilation in the face of a rising arterial carbon dioxide tension while low-flow oxygen is being administered.

Discussion

Arterial hypoxia, resulting from respiratory failure, can be relieved by increasing either the effectiveness of the ventilation or the concentration of inspired oxygen. Hypoxia develops from inefficiency of the diseased lung to deliver oxygen from the ambient air to the arterial blood. The effect of an increase in the inspired oxygen concentration on the arterial oxygen tension depends on the severity of the diseased lung. Hypoxemia in chronic obstructive pulmonary disease may occur with or without hypercapnia. Acute respiratory failure with hypoxemia necessitates oxygen supplementation; controlled oxygen therapy can be achieved with nasal cannula at 2 liters/min or with the Ventimask at 24% and 28%. Adequate monitoring is essential, as therapy with uncontrolled oxygen may seriously worsen ventilation. It has been shown that even a mildly elevated arterial carbon dioxide tension does not ensure against oxygen-induced hypoventilation.[14] An arterial oxygen tension of 50 mm Hg has been accepted as the minimal goal of oxygen therapy.[15] Both the nasal cannula and the Ventimask are well accepted by the patient. One disadvantage of the mask is that its use has to be interrupted for feeding and nebulization therapy.

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*See Test Your Word Score Page 933.

Oxygen therapy is obviously required. We must be aware of the potential risk of oxygen-induced hypoventilation. Hypoxemia may be severe from hypoventilation and also from venous admixture resulting from the pulmonary disease.

Effective management of oxygen therapy requires careful measurements of arterial oxygen tensions. In some cases the nasal cannula will be more helpful and in others the Ventimask. In still others, therapy with 100% oxygen may not result in an arterial oxygen saturation that is sufficient for function or survival.

Summary

Arterial hypoxia resulting from respiratory failure can be relieved by increasing the effectiveness of ventilation or the concentration of inspired oxygen.

Oxygen therapy in respiratory failure should be aimed at correcting the hypoxia to a safe

TABLE

Arterial Blood Gas Values in Chronic Obstructive Pulmonary Disease and Respiratory Failure

Case	Pa_{O_2}, mm Hg	Pa_{CO_2}, mm Hg	pH	O_2 saturation, %	Condition
1	44	56	7.41	80	Room air
	60	62	7.33	89	Nasal cannula, 2 L/min
	55	63	7.33	86	Ventimask, 24%
	96	80	7.27	96	Ventimask, 28%
	54	74	7.34	85	Ventimask, 24%
	59	73	7.35	89	Nasal cannula, 2 L/min
2	31	55	7.44	62	Room air
	37	52	7.43	72	Nasal cannula, 2 L/min
	39	60	7.40	73	Nasal cannula, 2 L/min
	47	60	7.38	82	Ventimask, 24%
	62	68	7.34	90	Ventimask, 28%
	62	62	7.39	92	Ventimask, 28%
3	65	38	7.47	94	Room air
	84	44	7.44	97	Nasal cannula, 2 L/min
4	35	56	7.26	57.5	On admission
	59	92	7.14	79	Nasal cannula, 2 L/min (7 hr later)
	97	57	7.30	96	Oral tracheal tube and controlled on Bird respirator (24 hr later)

level without enhancing the respiratory acidosis.

Two cases are presented to show the beneficial effects of controlled, low-flow oxygen by nasal cannula at 2 liters/min and by Ventimask at 24% and 28%. Both methods are effective in the administration of controlled, low-flow oxygen.

The third case illustrates how oxygen saturations from ear oximetry may not give a true picture in some patients and how controlled low-flow oxygen can be administered safely without the danger of hypercapnia. It also shows that hypoxemia may occur in chronic obstructive pulmonary disease without hypercapnia.

The fourth case is an example of low-flow oxygen being unsuccessful in relieving the hypoxemia because of a secretion problem, pneumonitis, and superimposed pulmonary congestion.

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Time

Here are the results of a survey conducted by a psychology class at the University of Wisconsin. If you live to be seventy or over, chances are that you will spend at least twenty years asleep. Two hours of your life will be taken up just punching a time clock or signing a time sheet for the twenty-five solid years of work you will do.

Golf, bowling and hiking will probably take up some of the seven years you are allowed for sports and walking. For five years you will shave and dress, and spend five months tying your shoes. Of the six-hundred-and-thirteen-thousand hours in your lifetime, a few over four thousand are allowed for playing cards. For seven years you will go to the movies, theater or other amusements. Another year will be spent at the telephone.

For two and a half years you will sit at a table, eating, and for another two and a half years you will smoke or chew gum.

The seventy-year life span includes three years of waiting, thirty hours annually looking in mirrors, and just for the record, you are allowed four hours a year for wiping your nose.

—Marion Pehowski, Journal of Living

Technique

Protocol for Cope Needle Pleural Biopsy*

Pleural biopsy should be considered in every patient with a pleural effusion in whom the cause is not apparent. This would exclude pleural biopsy when the effusion occurred as part of the clinical picture of congestive failure, cirrhosis, nephrosis, pneumonia, pulmonary embolus/infarct, collagen disease, and trauma to the involved hemithorax. The histologic picture tends to be non-specific in these conditions and no useful purpose is served by pleural biopsy. However, if the pleural fluid obtained on thoracentesis has the characteristics of an exudate (protein concentration of greater than 2.5 gm. %) when a transudate was expected, e.g., in congestive heart failure, a pleural biopsy should be performed as a primary diagnostic procedure at the time of initial thoracentesis. Lack of pleural effusion is not an absolute contraindication to performance of a pleural biopsy, but it does call for experienced personnel familiar with the technique.

Pre-Biopsy Workup

Roentgenologic

PA and lateral chest films are usually adequate and should be done within 24 hours of the biopsy. If the effusion is small or localized, obliques may be helpful.

Fluoroscopy may be necessary with small effusions and should be utilized freely with placement of markers to ascertain the most desirable biopsy site.

Hematology

History of bleeding tendency or recent administration of anticoagulant medications must be sought. Prothrombin time, bleeding and clotting time should be obtained, and occasionally platelet counts may be necessary.

Pre-medication

Barbiturates, depending upon the age and respiratory status of the patient, are advisable, since local anesthetics will be used.

Atropine, in a dose of 0.3 to 0.4 mg., should be given subcutaneously unless there is a specific contraindication. Atropine serves to prevent pleural shock, which is believed to be a vagal reaction.

Equipment, Materials

Preparation tray, medical thoracentesis tray and Cope biopsy needle are obtained; 1% Lidocaine, specimen jar with formalin, bottle with alcohol for cell block, and tube of culture medium should be at hand.

Position of Patient

This is usually sitting with arms and head supported against the examining table or bed; the patient must be comfortable. Localization of the effusion by physical diagnostic means should be done at this time. If there is any question as to the proper interspace, preference should be given to the upper one.

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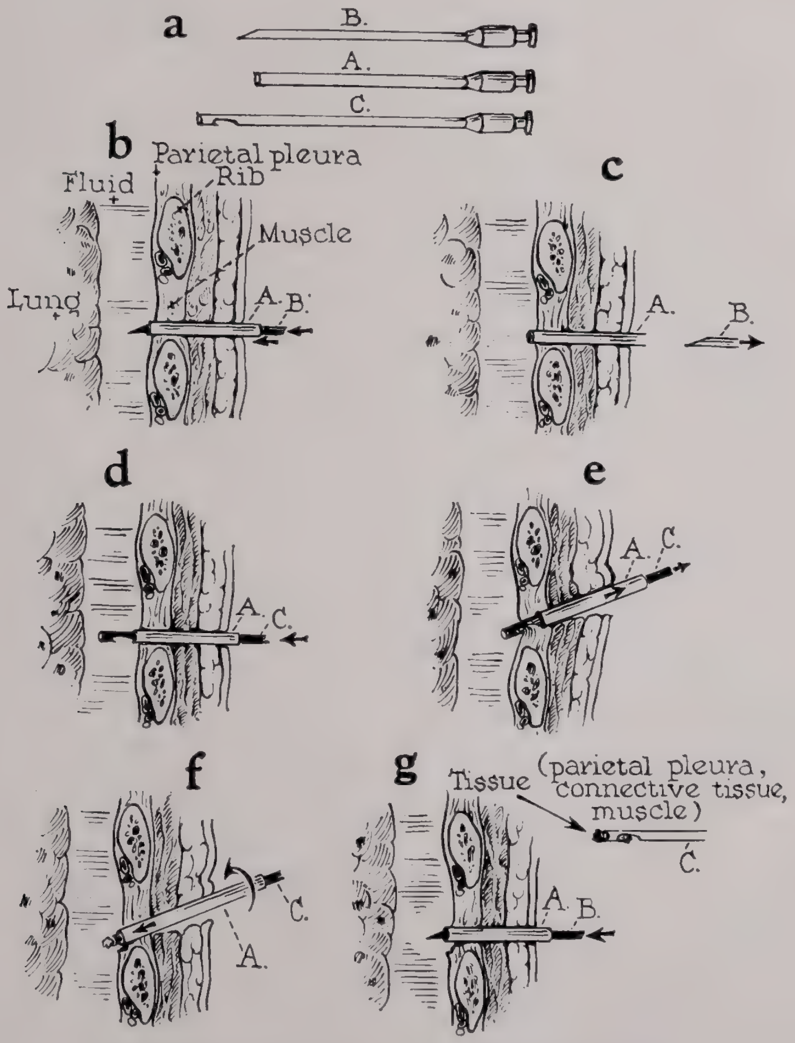
*See Grand Rounds: Needle of the Parietal Pleura, page 1011.

Preparation of the Site and Anesthesia

The usual preparation should be made, after which generous amounts of local anesthetic should be introduced. It is very important that complete anesthesia of the pleura be obtained. The cooperation of the patient in breath holding is required during the biopsy; a patient in pain is not likely to be cooperative. It is often recommended that the patient hold his breath when the infiltration needle is in the pleural space.

Withdrawal of Fluid

The outer cannula of the Cope needle is an excellent thoracentesis needle. Usually it is advisable to draw off sufficient fluid for all diagnostic tests prior to the performance of the biopsy, thereby avoiding the adulteration of the specimen by any bleeding which may be caused by the biopsy. If a very minimal amount of



Figure*—Components of Cope needle and method of use.

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*L. J. Kettel and D. W. Cugell's: Pleural Biopsy. JAMA 200:4:317, April 24, 1967 by permission of authors and JAMA.

fluid is present it may be advisable to do the biopsy initially.

Technique

The Cope needle is shown in Figure 1. The technique below is that described by Cope. The biopsy entails little morbidity and, since it is essentially a sampling procedure, at least three bites should be taken at each biopsy site. In fact, there is no contraindication to using two or three different biopsy sites at a single sitting. Pleural tissue is recognizable as white, yellowish-white, or gray-colored tissue attached to the red muscle invariably removed at biopsy. A biopsy attempt should not be concluded until such tissue is secured.

Using the Needle

Following local anesthesia and after the presence of fluid has been ascertained with a fine exploratory needle, the skin is nicked with a scalpel blade (No. 11); the 13-gauge needle, which is inserted within the cannula, is then slowly advanced with a twisting motion until fluid is aspirated in the connecting syringe; next, the inner needle is removed and the blunt-tipped hooked biopsy trochar, attached to a three-way stopcock, is quickly substituted within the cannula. If the cannula opening is covered by the left thumb between substitutions and the patient instructed to hold his breath and bear down during the needle exchange, little or no air will enter the chest. Sufficient fluid for diagnostic purposes is aspirated through the three-way stopcock. Both the cannula and the biopsy trochar are then slowly withdrawn *together*, while lateral pressure is applied in the direction of the hook, until the instrument is *felt* to catch the parietal wall; the right hand keeps a light but *steady traction* on the biopsy trochar while the left hand advances the outer cutting cannula with a rotating motion until the biopsy specimen, anchored within the hook, is sliced off and the instrument can be withdrawn.

The biopsy procedure is then repeated through the same skin incision with the hook biting in the opposite direction. Since needle biopsy is a sampling procedure, a total of three to five bites should be taken at two or more different sites at the same sitting, especially if the initial samples appear normal on gross examination. One or two pieces of tissue should be submitted for culture for tuberculosis and fungi. The pleural cavity is not completely drained of fluid until just before the last biopsy specimen is obtained. Once the correct technic is mastered, pleural tissue can be obtained with every bite.

Post-Biopsy Orders

Vital signs should be monitored at one-hour intervals for six hours. A post-biopsy chest film should be obtained within a few hours to detect hemothorax or pneumothorax.

Andrew E. Edin, M.D.
Minneapolis, Minnesota

All women become like their mothers. That is their tragedy. No man does. That is his.—Wilde

In peace, sons bury their fathers; in war, fathers bury their sons.—Herodotus

Minnesota Medicine at a Glance

Thioflavine-T—*Peterson and Gorlin* Page 899

Basal cell carcinoma and ameloblastoma show similarities in staining qualities, a tendency to be locally invasive and to recur if not adequately removed. The thioflavine-T positivity may be an amyloid-like mucopolysaccaride or a mucoprotein.

Corrosive Esophagitis—*Johnsen and Duvall* Page 909

Esophageal stricture, due to ingestion of corrosive substances, continues to be a common clinical problem. This occurs most commonly in mentally deficient individuals or in pediatric patients with neglectful parents. Additional cases arise following suicide attempts. The early use of antibiotics and steroids appears to reduce the inflammatory response and to prevent or minimize late stricture formation. Dilatation is often the treatment of choice. Surgery is sometimes necessary.

Tumors of the Upper Lip—*Abu Jamra et al.* Page 915

A statistical review of tumors of the upper lip treated at the Mayo Clinic from 1944 to 1963.

Placental Localization—*Meyer and Malkasian* Page 1001

The various techniques currently employed in placental localization are thoroughly discussed along with their respective advantages and disadvantages. These include localization by soft tissue x-ray, amniography, arteriography, intravenous placentography, isotopic placentography, thermography and ultrasound. The authors stress the fact that all of these give a high degree of accuracy (better than 90%) and that the selection of one over another depends upon available personnel and facilities.

Subinguinal Varix—*Lofgren* Page 1021

A subinguinal varix is caused by a swelling of the most proximal portion of the greater saphenous vein and is easily confused with a femoral hernia. While a hernia may not be reducible, a subinguinal varix will always disappear with finger pressure. The most reliable diagnostic sign is the transmission of a venous pulse either from the varix downward into the saphenous vein or from the saphenous vein into the varix. Associated varicose veins of the leg are commonly seen with this disorder. The treatment is surgical. The findings in eight women and two men with subinguinal varices are reviewed.

What's New

Burroughs-Wellcome & Company

The 1969 Passano award has been presented to George H. Hitchings, Ph.D., Vice-President in charge of research at Burroughs Wellcome & Company. The Passano award is made by the Passano Foundation, a nonprofit Maryland corporation devoted to the encouragement of medical science and research. Dr. Hitchings will receive this award in recognition of leadership in the application of the antimetabolite concept in the treatment of leukemia, gout and malaria and for immunosuppression.

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Thayer, Ellsworth A.	Fairmont
Virnig, Richard P.	Wells

PERMANENT EVALUATION

Carryer, H. M. (Chairman)	Rochester
Fawcett, K. R.	Duluth
Hall, Barnard	St. Paul
Hammar, L. M.	Mankato
McCarthy, Donald	Minneapolis
Paulson, Elmer	St. Paul
Stoy, Robert A.	Little Falls
Wasson, L. F.	Alexandria
Wellman, W. E.	Rochester
Wells, Walter B.	Jackson

PHYSICIANS' ASSISTANCE

Blake, James A. (Chairman)	Hopkins
Anderson, David W.	St. Paul
Boone, E. S.	Luverne
Bayley, E. Covell	Lake City
Boman, Paul G.	Duluth
Carlson, Carl E.	Alexandria
Dobson, M. W.	Mankato
Donaldson, C. S.	St. Cloud
Hoff, Herbert O.	Duluth
Jenson, James E.	Stillwater
Johnson, Douglas	Little Falls
Juergens, Herman M.	Belle Plaine
Kilbride, E. A.	Worthington
Macklin, W. E., Jr.	Litchfield
Schmidt, W. Robert	Minneapolis
Wilmot, Harold E.	Litchfield
Younger, Lewis	Winona

PROFESSIONAL LIABILITY

Wasson, L. F. (Chairman)	Alexandria
Anderson, Jo E.	LeSueur
Brigham, C. F.	St. Cloud
Drexler, George W.	Blue Earth
Floersch, A. J.	Owatonna
Jacobson, Clarence	Chisholm
Larson, Gerald	Cambridge
Miller, Harold E.	Minneapolis
Mosby, M. E.	Long Prairie
Schmid, John	Duluth

PUBLIC HEALTH EDUCATION

Sturley, R. F. (Chairman)	St. Paul

Executive Committee

Christensen, Norman A.	Rochester
Fliehr, Richard R.	Minneapolis
Fox, James Rogers	Minneapolis
Sturley, R. F.	St. Paul
Williams, George	St. Paul

Councilor District

Goldston, E. C. (1st)	Rochester
Boone, E. S. (2nd)	Luverne
Flinn, James B. (3rd)	Redwood Falls
Thiem, Chester (4th)	Mankato
Williams, George (5th)	St. Paul
Semsch, R. D. (6th)	Wayzata
Seifert, D. R. (7th)	Little Falls
Kuhlmann, V. G. (8th)	Alexandria
Jeronimus, Henry J., Jr. (9th)	Duluth

PUBLIC HEALTH NURSING

Wilson, Viktor O. (Chairman)	Minneapolis
Davis, Luther F.	Wadena
Fifer, Ellen Z.	St. Paul
Guy, Jack A.	New London
Hawley, George M. B., II	Red Wing
Houglum, Arvid J.	Duluth
Kitzberger, Peter J., Jr.	New Ulm
Knudsen, Helen L.	Minneapolis
Park, Wilford	Minneapolis

PUBLIC POLICY

Falls, John L., (General Chairman)	Red Wing

Councilor District

Spencer, R. J. (1st)	Rochester
Blumer, Arlo (2nd)	Albert Lea
Schnell, Frederick (3rd)	Litchfield
Wohlrabe, Donald (4th)	Springfield
Richardson, E. J., Jr. (5th)	St. Paul
Luh, Edwin F. (6th)	Minneapolis
Fitzsimons, W. E. (7th)	Brainerd
Wasson, Loren F. (8th)	Alexandria
Swenson, Arnold O. (9th)	Duluth

RESIDENCY COMMITTEE

Wellman, W. E. (Chairman)	Rochester
Ahmann, David	Rochester
Andreini, Paul H.	Rochester
Baumgartner, C. J., Jr.	Rochester
Blomberg, Robert D.	Minneapolis
Cavert, H. Mead	Minneapolis
Duane, Drake	Rochester
Hay, Lyle J.	Minneapolis
Janssen, Martin E.	St. Paul
Kane, Dennis	Minneapolis
Larson, Donald M.	Duluth
Lewis, F. Bruce	Minneapolis
McCarthy, Donald	Minneapolis
Raile, Richard B.	Minneapolis
Skogerboe, Rudolph	Minneapolis
Streitz, John M.	Duluth

RURAL MEDICINE SERVICE

Berg, A. M. (Chairman)	Thief River Falls
Councilor District	
Gjerde, W. P. (1st)	Lake City
Nywall, Dean D. (2nd)	Slayton
Brace, Ray I. (3rd)	Clinton
Lehrer, A. J. (4th)	Montgomery
Stratte, A. K. (5th)	Pine City
Yelle, Matthew D. (6th)	Anoka
Seifert, Donald R. (7th)	Little Falls
Berg, A. M. (8th)	Thief River Falls
Barnes, Richard E. (9th)	Aurora
Fuller, B. F., Jr.	Minneapolis
Harrison, William C.	Minneapolis
McCollister, Robert J.	Minneapolis
Nielsen, David J.	Minneapolis
Nolen, William A.	Litchfield
Sisk, Harvey E.	St. Cloud

SCHOLARSHIP & LOANS

Bartholomew, L. G. (Chairman)	Rochester
Christenson, Carl E.	Clinton
Engwall, Richard	Minnetonka
Fritsche, T. R.	New Ulm
Puumala, R. H.	Cloquet
Rutledge, John B.	Detroit Lakes

Sheppard, C. G.	St. Peter
Spencer, B. J.	Minneapolis

STATE HEALTH RELATIONS

Earl, John R. (Chairman)	St. Paul
Batdorf, B. Niles	Mankato
Bouquet, B. J.	Wabasha
Coe, John I.	Minneapolis
Grose, Frederick N.	Clarissa
Kilbride, E. A.	Worthington
Litman, S. N.	Duluth
Tesch, Gordon	Elk River
Votel, Thomas W.	St. Paul
Wilson, Viktor	Minneapolis

UNIVERSITY RELATIONS

Sheppard, C. G. (Chairman)	St. Peter
Buckley, R. P.	Duluth
Cosgriff, J. A., Jr.	Olivia
Huffington, H. L.	Waterville
Medelman, J. P.	St. Paul
Monahan, R. H.	St. Paul
Spencer, B. J.	Minneapolis
Spittell, J. A., Jr.	Rochester
Stickney, J. M.	Rochester
Wilder, Walter	Minneapolis

Councilor Districts

FIRST DISTRICT

G. R. Diessner, M.D. .... Rochester
Counties—Dodge, Fillmore, Goodhue, Houston, Mower, Olmsted, Rice, Steele, Wabasha, Winona.

SECOND DISTRICT

Mark P. Virnig, M.D. .... Wells
Counties—Cottonwood, Faribault, Freeborn, Jackson, Martin, Murray, Nobles, Pipestone, Rock, Watonwan.

THIRD DISTRICT

Williams A. Owens, M.D. .... Montevideo
Counties—Big Stone, Chippewa, Kandiyohi, Lac Qui Parle, Lincoln, Lyon, Meeker, Pope, Redwood, Renville, Stevens, Swift, Traverse, Yellow Medicine.

FOURTH DISTRICT

Wallace E. Mathews, M.D. .... Mankato
Counties—Blue Earth, Brown, Carver, Le Sueur, McLeod, Nicollet, Scott, Sibley, Waseca.

FIFTH DISTRICT

Barnard Hall, M.D. .... St. Paul
Counties—Anoka, Chisago, Dakota, Isanti, Kanabec, Mille Lacs, Pine, Ramsey, Sherburne, Washington.

SIXTH DISTRICT

Richard Frey, M.D. .... Minneapolis
Counties—Hennepin, Wright.

SEVENTH DISTRICT

Florian H. Baumgartner, M.D. .... Albany
Counties—Aitkin, Beltrami, Benton, Cass, Clearwater, Crow Wing, Hubbard, Lake of the Woods, Morrison, Stearns, Todd, Wadena.

EIGHTH DISTRICT

George A. Sather, M.D. .... Fosston
Counties—Becker, Clay, Douglas, Grant, Kittson, Mahnomen, Marshall, Norman, Otter Tail, Pennington, Polk, Red Lake, Roseau, Wilkin.

NINTH DISTRICT

John H. Peterson, M.D. .... Duluth
Counties—Carlton, Cook, Itasca, Koochiching, Lake, St. Louis.

COUNTY MEDICAL ADVISORY COMMITTEES

To County Welfare Boards

AITKIN COUNTY

George Pettersen	Aitkin
F. C. Closuit	Aitkin

ANOKA COUNTY

R. J. Spurzem	Anoka

BECKER COUNTY

E. S. Lorentzen	Detroit Lakes

BELTRAMI COUNTY

D. E. Hoganson	Bemidji
H. A. Palmer	Blackduck

BIG STONE COUNTY

Jacob F. Karn	Ortonville
Ray I. Brace	Clinton
Russell Popoff	Graceville

BLUE EARTH COUNTY

E. E. Heller	Mankato
D. H. Freeman	Mankato
W. E. Mathews	Mankato

BROWN COUNTY

T. R. Fritsche	New Ulm
L. Ringhofer	New Ulm
D. E. Wohlrabe	Springfield

CARLTON COUNTY

R. H. Puumala	Cloquet
Alvan Sach-Rowitz	Moose Lake

CARVER COUNTY

G. Nelson	Chaska

CASS COUNTY

C. R. Pelzl	Pine River
Carl H. Coombs	Cass Lake

CHIPPEWA COUNTY

H. A. Roust	Montevideo
T. G. Birkey	Montevideo

CHISAGO COUNTY

G. W. Hovde	Chisago City

CLAY COUNTY

R. A. Colliton	Moorhead

CLEARWATER COUNTY

L. J. Larson	Bagley

COOK COUNTY

Roger R. MacDonald	Grand Marais
Wallace R. Smith	Grand Marais

COTTONWOOD COUNTY

Alvin L. Wiens	Mountain Lake
J. H. Dokken	Windom
J. V. Carlson	Westbrook

CROW WING COUNTY

Albertus Dodson	Brainerd
J. B. Nixon	Crosby
Robert Poppie	Brainerd

DAKOTA COUNTY

Herman T. Fasbender	Hastings
John W. Foderick	Hastings

DODGE COUNTY

D. E. Affeldt	Kasson
Grant E. Olson	West Concord

DOUGLAS COUNTY

E. J. Tanquist, Sr.	Alexandria
Peter M. Geiser	Alexandria
J. H. Cain	Alexandria

FARIBAULT COUNTY

John W. Anderson	Blue Earth
J. A. Watkins	Wells
Donald E. Halvorson	Winnebago

FILLMORE COUNTY

J. E. Westrup	Lanesboro
Ralph B. Johnson	Lanesboro

COUNTY MEDICAL ADVISORY COMMITTEES

FREEBORN COUNTY

M. A. Keil	Albert Lea
G. A. Cole	Albert Lea
Harold Halvorson	Albert Lea
H. B. Neel	Albert Lea

GOODHUE COUNTY

G. F. Hartnagel	Red Wing
R. E. Molenaar	Cannon Falls

GRANT COUNTY

V. A. Doms	Elbow Lake

HENNEPIN COUNTY

Mark C. L. Hanson	Minneapolis
Charles A. Haberle	Minneapolis
Wayne C. Rydburg	Minneapolis
Sidney S. Scherling	Minneapolis
Nathan C. Plimpton	Minneapolis
Lester W. Carlander	Minneapolis
George W. Janda, Jr.	Minneapolis
Donald B. Frane	Minneapolis
Harold E. Miller—(Ex-officio)	Minneapolis

HOUSTON COUNTY

Hildegard J. Virnig	Caledonia
Philip Utz	LaCrescent
L. A. Knutson	Spring Grove

HUBBARD COUNTY

Norman R. Haugen	Park Rapids
Edgar R. Gamm	Park Rapids

ISANTI COUNTY

R. C. Magnuson	Cambridge

ITASCA COUNTY

Keith H. Stolen	Grand Rapids
Donald R. Mueller	Grand Rapids
Clarence R. Farrell	Grand Rapids

JACKSON COUNTY

V. W. Doman	Lakefield
H. A. Christiansen	Jackson
W. B. Wells	Jackson

KANABEC COUNTY

E. C. Burseth	Mora

KANDIYOHI COUNTY

John Docksey	Willmar
Lawrence Opsahl	Willmar
R. V. Hodapp	Willmar

KITTSON COUNTY

Roland Larter	Hallock

KOOCHICHING COUNTY

George M. Crow	International Falls
Frederick H. Walter	International Falls

LAC QUI PARLE COUNTY

Chester A. Anderson	Madison
V. M. Johnson	Dawson

LAKE COUNTY

G. E. Church	Two Harbors
Donald Haase	Silver Bay

LAKE-OF-THE-WOODS COUNTY

Allen G. Janecky	Baudette

LE SUEUR COUNTY

J. E. Anderson	Le Sueur
A. D. Walden	Le Sueur

LINCOLN COUNTY

C. O. Thompson	Hendricks
M. A. Muesing	Tyler

LYON COUNTY

K. A. Peterson	Marshall
W. Workman	Tracy

MAHNOMEN COUNTY

Charles B. Mercil	Mahnomen

MARSHALL COUNTY

Carle Holmstrom	Warren

MARTIN COUNTY

George N. Kraemer	Fairmont
H. A. Williamson	Fairmont

McLEOD COUNTY

John Smythe	Lester Prairie
Alvin M. Jensen	Brownton
Kenneth Peterson	Hutchinson

MEEKER COUNTY

Lennox Danielson	Litchfield
G. Olson	Litchfield
W. Nolen	Litchfield

MILLE LACS COUNTY

N. B. Metcalf	Princeton

MORRISON COUNTY

S. W. Watson	Little Falls
Milo Hansen	Little Falls
R. J. Stein	Pierz

MOWER COUNTY

Harold J. Anderson	Austin
T. M. Seery	Austin
H. Miller	Austin
W. L. Christian	Austin
Clifford Pesonon	Austin

MURRAY COUNTY

R. F. Pierson	Slayton
J. L. Bader	Slayton
H. D. Patterson	Slayton
Dean Nywall	Slayton

NICOLLET COUNTY

M. E. Lenander	St. Peter
Vern Olmanson	St. Peter
C. Wohlrabe	No. Mankato

NOBLES COUNTY

M. W. Plucker	Worthington
B. C. Faul	Worthington
D. J. Halpern	Brewster

NORMAN COUNTY

Byron Kinkade	Ada

OLMSTED COUNTY

Martin Van Herik	Rochester
James Doyle	Rochester
T. O. Wellner	Rochester
T. T. Myers	Rochester
Richard Steinhilber	Rochester
David Carr	Rochester
J. F. Fairbairn	Rochester

OTTER TAIL COUNTY

Carl J. Lund	Fergus Falls
Roy Nelson	Fergus Falls
C. W. Lewis	Henning
L. Syverson	Fergus Falls

PENNINGTON COUNTY

George Martin	Thief River Falls

PINE COUNTY

F. M. Mach	Pine City

PIPESTONE COUNTY

W. G. Benjamin	Pipestone
J. G. Lohmann	Pipestone
G. Beckering	Edgerton

POLK COUNTY

Howard Wikoff	Crookston

POPE COUNTY

Gordon E. Lee	Glenwood
Berton A. Kolp	Glenwood
Foster D. Bucher	Starbuck

RAMSEY COUNTY

Eugene E. Scott	St. Paul
J. L. Sprafka	St. Paul
P. F. W. Rick	St. Paul
E. C. Burklund	St. Paul
J. G. Fee	St. Paul
E. H. Karon	St. Paul
Eva Jane Larson	St. Paul
Alexander McEwan	St. Paul
Ralph Ramlow	St. Paul
R. J. Sells	St. Paul
J. F. Melancon	St. Paul
M. B. Sorem	St. Paul

RED LAKE COUNTY

Vincent Hunt	Red Lake Falls

REDWOOD COUNTY

S. Ceplecha	Redwood Falls
James B. Flinn	Redwood Falls
G. E. Nelson	Redwood Falls

RENVILLE COUNTY

C. A. Anderson	Hector
G. C. Bingham	Bird Island
Leo Furr	Bird Island

RICE COUNTY

Bernard Street	Northfield
Robert Speckhals	Faribault
Robert Meyers	Faribault
D. C. Halvorson	Northfield

ROCK COUNTY

Darrel Siebert	Luverne
F. W. Bofenkamp	Luverne
D. M. Odland	Luverne

ROSEAU COUNTY

Jack Delmore	Roseau

ST. LOUIS COUNTY

Karl Johnson	Duluth
R. P. Buckley	Duluth
W. H. Grohs	Duluth
J. P. Knoedler	Duluth
R. J. Thurn	Duluth
Richard R. Moyer	Hibbing
Raymond Martinson	Aurora
Frederic L. Mast	Chisholm
Stuart B. Walker	Aurora
Anthony Baraga	Hibbing
Charles Tietz	Virginia

COUNTY MEDICAL ADVISORY COMMITTEES

SCOTT COUNTY

P. J. Adams	Shakopee

SHERBURNE COUNTY

G. H. Tesch	Elk River

SIBLEY COUNTY

A. F. Dysterheft	Gaylord
J. E. Schroeppel	Winthrop
R. H. Kath	Arlington

STEARNS-BENTON COUNTY

J. N. Olinger	St. Cloud
C. D. Stiles	Foley
John Kelly	Cold Spring
Severin Koop	St. Cloud
R. J. Cumming	St. Cloud

STEELE COUNTY

A. J. Floersch	Owatonna
T. W. Stransky	Owatonna
R. W. deWerd	Owatonna

STEVENS COUNTY

R. A. Rossberg	Morris
O. A. Eide	Hancock
Robert Watson	Morris

SWIFT COUNTY

Joseph Rorem	Appleton
N. Wagner	Benson
T. S. Eberley	Benson

TODD COUNTY

Alvin Erickson	Long Prairie
F. N. Grose	Clarissa

TRAVERSE COUNTY

A. E. Magnuson	Wheaton
H. C. Winge	Wheaton

WABASHA COUNTY

W. P. Gjerde	Lake City
E. W. Ellis	Elgin
R. N. Bowers	Lake City

WADENA COUNTY

Leland Reichelt	Wadena
W. E. Parker	Sebeka
W. B. Halme	Wadena

WASECA COUNTY

O. J. Swenson	Waseca
N. P. Cabot	Waseca

WASHINGTON COUNTY

James E. Jenson	Stillwater
F. M. McCarten	Stillwater

WATONWAN COUNTY

R. A. Parsons	St. James
Herbert Boysen	Madelia

WILKIN COUNTY

L. O'Brien	Breckenridge
C. W. Jacobson	Breckenridge
Neil Kippen	Breckenridge

WINONA COUNTY

Herbert vR. Heise	Winona
Robert B. Tweedy	Winona
Henry J. Roemer	Winona

WRIGHT COUNTY

Lester Bendix	Annandale
Pierre J. Guilfoile	Delano

YELLOW MEDICINE COUNTY

C. L. Lundell	Granite Falls
Olin M. Odlund	Granite Falls

Woman's Auxiliary to the Minnesota State Medical Association

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Mrs. Cyril Tifft	President-elect	St. Paul
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Mrs. L. L. Bissinger	Second Vice President	Brainerd
Mrs. Richard C. Horns	Third Vice President	Edina
Mrs. D. R. Gillespie	Fourth Vice President	St. Paul
Mrs. Edwin S. Boone	Recording Secretary	Luverne
Mrs. John Dwyer	Corresponding Secretary	Duluth
Mrs. Robert Hebbel	Treasurer	St. Paul
Mrs. Charles Steinberg	Auditor	St. Paul
Mrs. John H. Peterson	Historian	Duluth
Mrs. M. F. Fellows	Parliamentarian	Duluth

Regional Advisors

Mrs. D. C. Dahlin	First District	Rochester
Mrs. William Halvorson	Second District	Madelia
Mrs. James A. Cosgriff	Third District	Olivia
Mrs. Wynn Kearney	Fourth District	Mankato
Mrs. Edgar Burseth	Fifth District	Mora
Mrs. John Linner	Sixth District	Minneapolis
Mrs. L. L. Bissinger	Seventh District	Brainerd
Mrs. Arthur Sethre	Eighth District	Fergus Falls
Mrs. John Barker	Ninth District	Duluth

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Bylaws—Mrs. G. R. Diessner	Rochester
Community Health—Mrs. Kenneth Lerdahl	St. Paul
Pre-School Medical Survey of Vision and Hearing and Committee for the Aging—Mrs. Chauncey Kelsey	St. Paul
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International Health Activities—Mrs. Richard C. Horns	Edina
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Program—Mrs. Howard Andersen	Rochester
AMA-ERF—Mrs. M. I. Shelander	St. Paul
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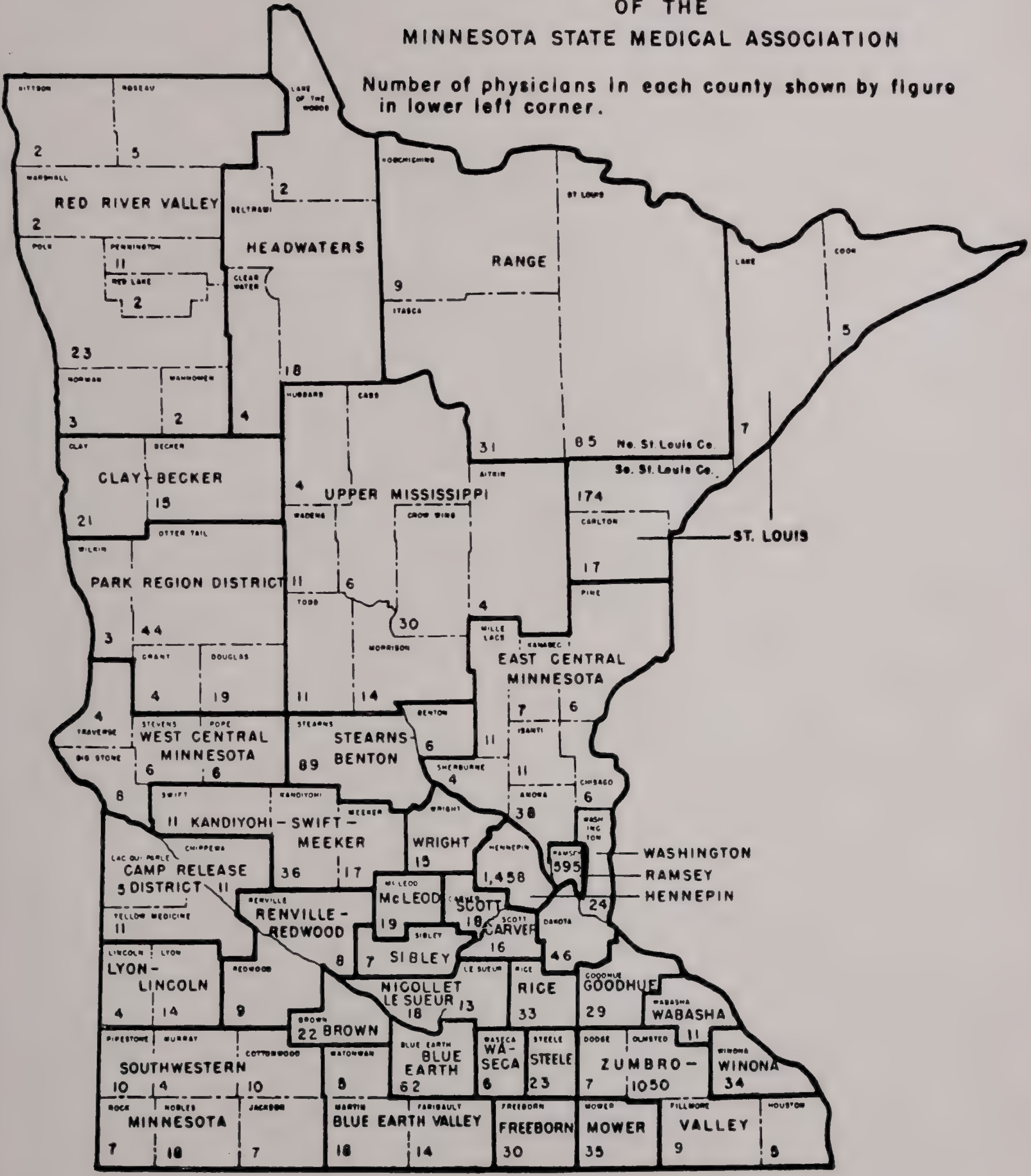
Membership—Mrs. Cyril Tifft	St. Paul
WA/SAMA Liaison—Mrs. Herman Drill	Hopkins
Editor—Gopher Doctor's Wife—Mrs. Rolf Andreassen	Minneapolis
Press and Publicity—Mrs. Byron Cochrane	St. Paul
Roster—Mrs. W. P. Gjerde	Lake City
Resolutions—Mrs. Leo Fink	Minneapolis
Fall School of Instruction—	
Mrs. George Tani (Chairman)	St. Paul
Mrs. John Rukavina	St. Paul
Mrs. Clarence J. Rowe	St. Paul
Mrs. E. C. Menefee	Albert Lea
Mid-Winter Board Meeting—	
Mrs. Charles Lindemann	Edina
Mrs. Richard C. Tucker	Edina
Mrs. Anthony Pollock	Edina
Mrs. A. Don Walden	Le Sueur
Advisory Committee—	
Mrs. Walter P. Gardner	St. Paul
Mrs. W. A. Merritt	Rochester
Mrs. M. I. Hauge	Marcell
Mrs. F. W. Conley	Duluth
Mrs. F. G. Gunlaugson	Minneapolis

COUNTY MEDICAL SOCIETIES
OF THE
MINNESOTA STATE MEDICAL ASSOCIATION

Number of physicians in each county shown by figure in lower left corner.


RED RIVER VALLEY
2
5
2
11
2
23
3
2
HEADWATERS
2
18
4
RANGE
9
31
85 No. St. Louis Co.
So. St. Louis Co.
174
17
ST. LOUIS
7
5
CLAY-BECKER
21
15
UPPER MISSISSIPPI
4
PARK REGION DISTRICT
11
6
3
44
30
4
4
19
11
14
EAST CENTRAL MINNESOTA
7
6
WEST CENTRAL MINNESOTA
4
6
6
8
STEARNS-BENTON
89
6
11
4
11
38
6
11 KANDIYOHI-SWIFT-MEEKER
36
17
WRIGHT
15
CAMP RELEASE DISTRICT
5
11
11
1,458
595
24
WASHINGTON
RAMSEY
HENNEPIN
RENVILLE-REDWOOD
8
McLEOD
19
SCOTT
18
CARVER
16
46
SIBLEY
7
LYON-LINCOLN
4
14
9
NICOLLET LE SUEUR
18
13
RICE
33
GOODHUE
29
WABASHA
11
BROWN
22
SOUTHWESTERN
10
4
10
8
BLUE EARTH
62
WA-SECA
6
STEELE
23
ZUMBRO-
7
1050
WINONA
34
MINNESOTA
7
18
7
BLUE EARTH VALLEY
18
14
FREEBORN
30
MOWER
35
VALLEY
9
5

County Medical Society Roster

KEY TO SYMBOLS AS FOLLOWS
* Deceased
† Affiliated, Associated, Life, or Resident Members
# Service
‡ Wife is Member of Woman's Auxiliary
¶ Honorary Member

BLUE EARTH COUNTY MEDICAL SOCIETY

Blue Earth County
Regular meetings, fourth Monday of the month
Annual meeting, December
Number of members 60

	PRESIDENT	
	Scheidel, A. M.	Mankato
	SECRETARY	
	Grande, D. W.	Mankato
‡	Anderson, Oscar D.	Mankato
	Aquilina, Joseph N.	Mankato
‡	Arnesen, Paul M.	Mankato
‡	Barbarisi, Charles F.	Mankato
‡	Batdorf, B. Niles	Mankato
	Brady, Charles H.	Mankato
†	Butzer, John A.	Mankato
‡	Chalgren, William S.	Mankato
‡	Conley, Robert H.	Mankato
	Dobson, Mervin W.	Mankato
‡	Edwin, R. L.	No. Mankato
	Eckert, Joseph F.	Mankato
‡	Eisenbeis, C. F.	Mankato
	Elliott, J. W.	Mankato
	Engstrom, Robert B.	Mankato
	Eustermann, John J.	Mankato
‡	Flentje, Dale E.	Mankato
‡	Florine, Martin C.	Madison Lake
‡	Fortier, R. G.	Mankato
†	Franchere, Frederick W.	Lake Crystal
‡	Geurs, Benjamin R.	Mankato
‡	Gislason, Paul H.	Mankato
‡	Grande, David W.	Mankato
‡	Hammar, Lawrence M.	Mankato
	Hankerson, Robert G.	Mankato
‡	Heimark, John J.	Mankato
‡	Heller, Edgar E.	Mankato
‡	Hoeper, Philip G.	Mankato
	Huffington, Herb L.	Waterville
†	Huffington, Herbert L.	Lutsen
	Jones, Orville H.	Mankato
‡	Kearney, R. Wynn	Mankato
†	Kemp, Alphonse F.	Mankato
	La Brec, H. C.	Mankato
	Lester, John W.	Mapleton
‡	Lindblom, Alton E.	No. Mankato
†	Luck, Hilda	Mankato
‡	Lund, J. Benjamin	Mankato
	McBride, Alexander M.	Mankato
‡	Marso, John L.	Mankato
‡	Mathews, Wallace E.	Mankato
‡	Meredith, Donald C.	Mankato
‡	Mickelson, John C.	Los Angeles, CA
	Morgan, Hugh O.	Amboy
	Penn, George E.	Mankato
‡	Roth, Frederick D.	Mankato
‡	Sanford, Raymond A.	Mankato
‡	Scheidel, A. M.	Mankato
‡	Schmitz, Anthony A.	Mankato
‡	Setzer, Hobert J., Jr.	Mankato
‡	Sjoding, J. Donald	Mankato
‡	Smith, Harry J.	Lake Crystal
	Stillwell, Walter C.	Mankato
‡	Swenson, Donald B.	Mankato
‡	Thiem, Chester E.	Mankato
†	Troost, H. Bradley	Mankato
†	Vezina, John C.	Mapleton
‡	Von Drasek, Joseph	Mankato
‡	Wahl, Donald H.	Mankato
†	Wentworth, Albert J.	Mankato

BLUE EARTH VALLEY MEDICAL SOCIETY

Martin, Watonwan and Faribault Counties
Regular meetings, third Wednesday of each month
Annual meeting in November
Number of members 40

	PRESIDENT	
	Lester, Malcolm J., Jr.	Truman
	SECRETARY	
	Boysen, Herbert	Madelia
‡	Anderson, John W.	Blue Earth
	Armstrong, Ralph S.	Winnebago
‡	Bellomo, John	Fairmont
*†‡	Bergman, Oscar B.	St. James
‡	Boysen, Herbert	Madelia
†	Bratrude, Earl J.	Hopkins
	Cox, Russell L.	Estherville, IA
‡	Drexler, George W.	Blue Earth
‡	Feigal, William M.	Fairmont
‡	Gardner, Jack K.	Fairmont
†	Gardner, Victor H.	Fairmont
	Halverson, Donald E.	Winnebago
‡	Halverson, William G.	Madelia
‡	Hanson, Lewis	Frost
	Hruza, William J.	Sioux Falls, SD
	Kraemer, George N.	Fairmont
	Krause, Carl W.	Fairmont
	Lester, Malcolm J., Jr.	Truman
	Lindahl, Merlyn J.	Sherburn
‡	Mattson, Albert D.	St. James
†	Mills, John L.	Winnebago
‡	Moulton, Keith B.	St. James
‡	Nickerson, John R.	Fairmont
‡	Nickerson, Neil D.	Fairmont
†‡	Ourada, Anthony L.	St. Paul
‡	Parsons, R. A.	St. James

Blue Earth Valley Medical Society (*Continued*)

	Parsons, Ralph L.	Trimont
	Pitcher, Arlo L.	St. James
‡	Russ, Homer H.	Blue Earth
	Schotzko, John R.	Blue Earth
	Schulz, Robert W.	Fairmont
	Smith, Don V.	Blue Earth
‡	Snyder, Clifford D.	Kiester
‡	Thayer, Ellsworth A.	Fairmont
‡	Virnig, Mark P.	Wells
‡	Virnig, Richard P.	Wells
	Wandke, Otto E.	Fairmont
	Watkins, John A.	Wells
‡	Williamson, Harold A.	Fairmont
‡	Zemke, Erhart E.	Fairmont
‡	Zemke, Robert L.	Fairmont

BROWN COUNTY MEDICAL SOCIETY

Brown County
Regular meetings, quarterly,
January, April, July, and October
Annual meeting in January
Number of members 25

PRESIDENT

	Kaiser, Milton L.	New Ulm

SECRETARY

	Ringhofer, Lawrence	New Ulm
‡	Black, William A.	New Ulm
‡	Boyle, Francis J.	Springfield
‡	Burnett, Joseph W.	New Ulm
‡	Cairns, Robert J.	Redwood Falls
‡	Carthey, Frank J.	New Ulm
‡	Fesenmaier, Otto B.	San Gabriel, CA
†	Fritsche, Albert	New Ulm
‡	Fritsche, Carl J.	New Ulm
‡	Fritsche, Theodore R.	New Ulm
	Goblirsch, Andrew P	Sleepy Eye
‡	Johnson, Rex R	New Ulm
‡	Kaiser, Milton L	New Ulm
‡	Keithahn, Elmer E.	Sleepy Eye
‡	Kitzberger, Peter J.	New Ulm
	Muesing, William J.	New Ulm
†	Nuessle, Walter G.	Springfield
‡	Penk, Engward L.	Springfield
	Peterson, Roy A.	Vesta
‡	Rimas, Mathew J.	Comfrey
‡	Ringhofer, Lawrence	New Ulm
‡	Saffert, Cornelius A.	New Ulm
	Vogel, Howard A. L.	New Ulm
	Wing, Elton G.	Sleepy Eye
	Wohlrabe, Donald E.	Springfield
‡	Wohlrabe, Edwin J.	Springfield

CAMP RELEASE DISTRICT MEDICAL SOCIETY

Chippewa, Lac qui Parle and Yellow Medicine Counties
Regular meetings, second Thursday of each month
except July and August
Annual meeting, November
Number of members 24

PRESIDENT

	Hagberg, Norman L.	Montevideo

SECRETARY

	Kremer, Jerome L.	Montevideo
‡	Allen, John H.	Montevideo
‡	Anderson, Chester A.	Madison
‡	Birkey, Thomas G.	Montevideo
‡	Boody, George J.	Cambridge
‡	Burns, Floyd M.	Milan
†	Burns, M. A.	Milan
‡	Camp, Ray J.	Madison
‡	Gustafson, Robert W.	Granite Falls
‡	Hagberg, Norman L.	Montevideo
†‡	Hauge, Malvin I.	Marcell
‡	Johnson, Vilhelm M.	Dawson
†	Jordan, Kathleen B. Smith	Granite Falls
‡	Karrow, John W.	Granite Falls
†‡	Kaufman, William C.	Appleton
‡	Kremer, Jerome L.	Montevideo
‡	Lima, Ludvig R.	Montevideo
‡	Lundell, Carl L.	Granite Falls
‡	Maus, Philip W.	Dawson
‡	Niazi, Suad A.	Granite Falls
‡	Odland, Olin M.	Granite Falls
‡	Owens, William A.	Montevideo
	Roust, Henry A.	Montevideo
‡	Schmidt, Paul G.	Granite Falls
‡	Westby, Norval M.	Madison

CLAY-BECKER COUNTY MEDICAL SOCIETY

Clay and Becker Counties
Regular meeting date, April
Annual meeting, November
Number of members 28

PRESIDENT

	Covey, K. W.	Moorhead

SECRETARY

	Saxman, Gertrude O.	Ulen

	Bigler, Earl E.	Perham
	Bigler, Ivan E.	Perham
	Bologna, Camillo V.	Moorhead
†	Bottolfson, B. T.	Moorhead
‡	Brenk, Paul E.	Detroit Lakes
	Carlon, Donald L.	Moorhead
	Carlson, Vernon J.	Moorhead
	Colliton, Patrick A.	Moorhead
‡	Covey, Kenneth W.	Moorhead
‡	Dodds, William C.	Detroit Lakes
‡	Duncan, James W.	Moorhead
‡	Geib, Marvin J.	Fargo, ND
‡	Holten, John	Moorhead
	Johnson, Olga H.	Moorhead
‡	Knapp, James F.	Detroit Lakes
	Koons, William R.	Mahnomen
‡	Lorentzen, Ernest S.	Detroit Lakes
‡	Midthune, Andreen S.	Lake Park
*‡	Moberg, Clarence W.	Detroit Lakes
	Norberg, William J.	Lake Park
	Odland, Mark E.	Detroit Lakes
‡	Rice, Hagbart G.	Moorhead
‡	Rutledge, John B.	Detroit Lakes
†‡	Rutledge, Lloyd H.	Detroit Lakes
	Saxman, Gertrude O.	Ulen
‡	Simison, Carl	Barnesville
‡	Thysell, Vernon D.	Moorhead
‡	Watson, Robert N.	Detroit Lakes
‡	Watson, Virgil A.	Detroit Lakes

EAST CENTRAL MINNESOTA MEDICAL SOCIETY

Anoka, Chisago, Isanti, Kanabec, Mille Lacs,
Pine and Sherburne Counties
Regular meetings first Tuesday of even
months of the year
Annual meeting, first Tuesday in December
Number of members 36

PRESIDENT

	Deason, Keith	Chisago City

SECRETARY

	Sommer, Robert K.	Elk River

	Ahlstrom, Robert C.	Braham
	Aruguete, Alayne	Sandstone
	Aruguete, Jose	Sandstone
	Berge, Harry L.	Mora
	Berglund, Alvin E.	Cambridge
	Brettingen, Larry J.	Mora
	Bunker, Bevan W.	Anoka
‡	Burseth, Edgar C.	Mora
‡	Deason, Keith B.	Chisago City
	Doebler, Myron I.	Mora
	Gailitis, Veronika M.	St. Paul
	Grinvalds, Anna O.	Cambridge
*	Halpin, Joseph E.	Rush City
‡	Hovde, Gordon W.	Chisago City
	Huber, Robert W.	St. Croix Falls, WI
	Hubin, Edwin G.	Sandstone
†	Kelsey, Carleton G.	St. Paul
	Lamusga, David J.	Mora
	Larson, Gerald E.	Cambridge
‡	Lindquist, Dale C.	Lindstrom
*‡	McManus, William F.	Albuquerque, NM
	Mach, Ralph F.	Pine City
	Magnuson, Raymond C.	Cambridge
	Nelson, Luther A.	Rush City
‡	Nordman, Willard F.	Mora
	Nygren, William T.	Braham
	Peterson, Alvin C.	Mora
	Pivac (Popovich) Dragojla	Milwaukee, WI
	Reiners, Gary	Cambridge
	Sander, John L.	Cambridge
†	Schut, John W.	Anoka
	Seecamp, Carsten H.	Cambridge
	Sommer, Robert K.	Elk River
†	Spurzem, Raymond J.	Anoka
†‡	Stratte, Alf K.	Pine City
‡	Swenson, Roy G.	North Branch

FREEBORN COUNTY MEDICAL SOCIETY

Freeborn County
Regular meetings, third Thursday of even months
Annual meeting, December
Number of members 35

PRESIDENT

	Steiner, Leon E.	Albert Lea

SECRETARY

	Ellertson, Leonard M.	Albert Lea

‡	Barr, Lowell C.	Albert Lea
‡	Barr, Lowell W.	Albert Lea
‡	Bartness, John E.	Albert Lea
‡	Blumer, Arlo R.	Albert Lea
†	Burns, Catherine	Excelsior
†	Calhoun, Frank W.	Albert Lea
‡	Campbell, John C.	Albert Lea
	Cole, George A.	Albert Lea
‡	Demo, Robert A.	Albert Lea

Freeborn County Medical Society (*Continued*)

	Donovan, Daniel L.	New Brighton
‡	Egge, Sanford G.	Albert Lea
‡	Ellertson, Leonard M.	Albert Lea
	Erdal, Ove A.	Big Spring, TX
‡	Gamble, Elbert J.	Roseville
‡	Gill, Theodore M.	Albert Lea
‡	Halvorson, Harold C.	Albert Lea
‡	Hansen, Theodore M.	Albert Lea
‡	Keil, Marcus A.	Albert Lea
†	Leopard, Brand A.	Brownsville, TX
‡	Menefee, Edward C.	Albert Lea
‡	Myers, Theodore P.	Albert Lea
‡	Neel, Harry B.	Albert Lea
‡	Nelson, Clayton E. J.	Albert Lea
‡	Nesheim, Martin O.	Emmons
‡	Palmer, Clinton F.	Albert Lea
‡	Schmidt, Ruben F.	Alden
‡	Shepard, Richard	Albert Lea
‡	Sherman, Alfred G.	Albert Lea
‡	Steiner, Leon E.	Albert Lea
‡	Stoker, Lynn C.	Albert Lea
‡	Treanor, Thomas A.	Albert Lea
‡	Whitson, Sidney A.	Albert Lea
‡	Wilcox, G. Charles	Albert Lea
‡	Willie, James A.	Albert Lea

GOODHUE COUNTY MEDICAL SOCIETY

Goodhue County
Regular meeting, April and November
Annual meeting, December
Number of members 26

	PRESIDENT	
	Nicolay, William R.	Red Wing
	SECRETARY	
	Wasmund, C. W.	Red Wing
‡	Akins, Willard M.	Red Wing
‡	Billings, Harry H.	Red Wing
†	Brusegard, James F.	Red Wing
‡	Cant, Wilbur F.	Red Wing
‡	Delahunty, John R.	Red Wing
	Douglass, Jesse E.	Cannon Falls
	Falls, John L.	Red Wing
	Friedrich, Bradford E.	Red Wing
‡	Halvorson, James W.	Zumbrota
‡	Hartnagel, Grant F.	Red Wing
‡	Hawley, George M. B.	Red Wing
‡	Jackish, George E.	Red Wing
‡	Juers, Edward H.	Red Wing
‡	Larson, Oliver E. H.	Zumbrota
†‡	Liffrig, William W.	Red Wing
‡	Molenaar, Robert E.	Cannon Falls
	Nicolay, William R.	Red Wing
‡	Rayner, Ralph R.	Red Wing
‡	Roth, Charles W.	Red Wing
	Schroeder, Glenn E.	Red Wing
‡	Sherman, Royal V.	Red Wing
†‡	Steffens, Leon	Red Wing
‡	Walter, William E.	Wanamingo
‡	Wasmund, Clarence W.	Red Wing
	Williams, Harry J., III	Red Wing
‡	Williams, Marland R.	Cannon Falls

HEADWATERS MEDICAL SOCIETY

Beltrami, Clearwater and Lake of the Woods Counties
Regular meetings, to be determined
Annual meeting, 2nd Saturday in September
Number of members 24

	PRESIDENT	
	Whittemore, D. D.	Bemidji
	SECRETARY	
	Groschupf, Richard P.	Bemidji
	Brink, Adlai A.	Baudette
	Deweese, Wilford J.	Bemidji
	Franklin, Gordon W.	Northome
	Gregoire, Earl	Bemidji
	Griffin, John W.	Bemidji
	Groschupf, Richard P.	Bemidji
†	Groschupf, Theophilus P.	Bemidji
	Hartjen, Jason K.	Bemidji
	Hildebrand, John E.	Bemidji
	Hoganson, Donald E.	Bemidji
	Janecky, Allen G.	Baudette
†	Johnson, Einer W.	Bemidji
	LaLonde, John B.	Bemidji
	Larson, Leroy J.	Bagley
	Lundsten, Leslie C.	Bemidji
	Martin, Frederick F.	Bagley
	Palmer, Harry A.	Blackduck
	Pearson, Harris L.	Bagley
	Reeber, Erick	Bagley
	Reid, Howard	Bemidji
	Roholt, Hartvig B.	Bemidji
	Thompson, James R.	Bemidji
	Whittemore, Dexter D.	Bemidji
	Wohlfiel, Dwayne L.	Bemidji

HENNEPIN COUNTY MEDICAL SOCIETY

Hennepin County
Regular meetings, first Monday of the Months of
October, January, March and May, except when
otherwise designated
Annual meeting, first Monday in October
Number of members 1408

PRESIDENT

Anonsen, Richard E. .... Minneapolis

SECRETARY

Mankey, James C. .... Minneapolis

EXECUTIVE SECRETARY

Cook, Thomas P., Mr. .... Minneapolis

‡	Abramson, Burton I.	Minneapolis
#	Abramson, Michael B.	Oakland, CA
	Abramson, Milton	Minneapolis
‡	Abullarade, Jose A.	Minneapolis
‡	Abuzzahab, Faruk S.	Minneapolis
‡	Adams, Brandon, L. W.	Minneapolis
	Adams, Richard I.	Minneapolis
‡	Adkins, C. Douglas	Minneapolis
‡	Adkins, James T.	Coon Rapids
	Adicoff, Arnold	Minneapolis
‡	Agustsson, Hreidar	Minneapolis
‡	Ahern, Eugene E.	Minneapolis
	Akbar, Sajady	Minneapolis
	Alari, Heino	Excelsior
‡	Alexander, Harlan A.	Minneapolis
‡	Aling, Charles A.	Minneapolis
‡	Allen, James R.	Minneapolis
	Alter, Milton	Minneapolis
†	Altnow, Hugo O.	Coral Gables, FL
‡	Amatuzio, Donald S.	Minneapolis
‡	Amren, Don P.	Minneapolis
	Andregg, Alfred F.	St. Paul
‡	Andersen, James G.	Minneapolis
	Andersen, Robert C.	Minneapolis
‡	Anderson, Arnold S.	Minneapolis
‡	Anderson, David M.	Minneapolis
‡	Anderson, Ernest R.	Minneapolis
‡	Anderson, Frank J.	Minneapolis
	Anderson, John A.	Minneapolis
	Anderson, John R.	Minneapolis
†‡	Anderson, Karl W.	Excelsior
	Anderson, Roger E.	Minneapolis
‡	Anderson, Roger L.	Minneapolis
	Anderson, Thomas P.	Minneapolis
	Anderson, U. Schuyler	Minneapolis
	Anderson, Wallace E.	Minneapolis
	Anderson, Wallace R.	Minneapolis
‡	Anderson, William H.	Minneapolis
	Anderson, William T.	Minneapolis
	Anderson, W. Robert	Minneapolis
	Andre, James C.	Minneapolis
†‡	Andreassen, Einar C.	Minneapolis
‡	Andreassen, Rolf L.	Minneapolis
‡	Andresen, Karl d'A	Minneapolis
‡	Ankner, Frank J.	Minneapolis
‡	Anonsen, Richard E.	Minneapolis
	Anselment, Lois A.	Excelsior
†	Arends, Archabald L.	Minneapolis
‡	Arey, Stuart Lane	Minneapolis
‡	Arhelger, Stuart W.	Minneapolis
‡	Arlander, Clarence E.	Minneapolis
‡	Arms, James J.	Minneapolis
	Armstrong, Byron H.	Minneapolis
†	Arnold, Ann W.	Minneapolis
	Arnold, Thomas B.	Minneapolis
‡	Aughenbaugh, John W.	Minneapolis
†	Aust, John C.	Minneapolis
	Avant, Robert F.	Minneapolis
	Azad, A. M.	Minneapolis
‡	Baggenstoss, Osmond J.	Minneapolis
‡	Bagley, Russell W.	Minneapolis
†‡	Baken, Melvin P.	Minneapolis
	Baken, Melvin P., Jr.	Minneapolis
	Baker, Abe B.	Minneapolis
‡	Baker, C. Camak	Minneapolis
†	Baker, Daniel R.	Minneapolis
‡	Baker, Milton E.	Minneapolis
	Bakke, Arnold C.	Minneapolis
‡	Balkin, Samuel G.	Minneapolis
	Balkins, John W.	Minneapolis
‡	Balogh, Charles J.	Minneapolis
	Bandt, Calvin M.	Minneapolis
†	Bank, Harry E.	Minneapolis
	Banovetz, John D.	Minneapolis
‡	Barnett, Robert M.	Minneapolis
‡	Barno, Alex	Minneapolis
‡	Barr, Maxwell M.	Minneapolis
	Barr, Robert N.	Minneapolis
	Barrett, Patrick J.	Minneapolis
‡	Barron, Jesse J.	Minneapolis
†‡	Barron, Moses	Beverly Hills, CA
‡	Barry, George J.	Edina
	Bart, Bruce J.	Minneapolis
‡	Beach, Northrop	Minneapolis
	Beard, Archibald H., Jr.	Minneapolis
†	Becker, Arnetta M.	Minneapolis
‡	Becklund, Roger W.	Minneapolis
	Beeman, John A.	Minneapolis
‡	Beirstein, Samuel	Minneapolis
‡	Beiswanger, Richard H.	Minneapolis
‡	Bell, Donald C.	Minneapolis
	Bellville, Titus P.	Minneapolis
‡	Belzer, Meyer S.	Minneapolis
	Bendel, Richard P.	Minneapolis
	Bendel, William L., Jr.	Coon Rapids
	Benesh, Louis A.	Minneapolis
‡	Benjamin, Edwin G.	Minneapolis
‡	Benjamin, Harold G.	Minneapolis
	Benjamin, Richard D.	Minneapolis
‡	Benjamin, Robert B.	Minneapolis
	Bentz, Herman D.	Anoka
‡	Berestka, Stephen J.	Minneapolis
	Berg, Clinton C.	Excelsior
	Berger, Alex G.	Minneapolis
‡	Bergh, George S.	Minneapolis
	Bergh, Solveig M.	Minneapolis
‡	Berglund, Eldon B.	Minneapolis
‡	Bergquist, James R.	Minneapolis
	Bergstrom, Ralph W., Jr.	Maple Plain
†	Bergstrom, William J.	Minneapolis
‡	Berkwitz, Nathaniel J.	Minneapolis
	Berman, David A.	Minneapolis
	Berman, Reuben	Minneapolis
	Bernstein, Dorothy M.	Minneapolis

Hennepin County Medical Society *(Continued)*

	Bernstein, Eugene F.	Minneapolis
	Bernstein, Irving C.	Minneapolis
‡	Berris, Harold	Minneapolis
‡	Berry, Ronald N.	Minneapolis
	Berzins, Rainis	Minneapolis
†‡	Bessesen, Alfred N.	Minneapolis
‡	Bevis, William D.	Minneapolis
	Bieter, Raymond N.	Minneapolis
	Bilgutay, Aydin M.	Minneapolis
	Bilka, Paul J.	Minneapolis
	Billman, Herbert R.	Minneapolis
‡	Binder, Manuel R.	Minneapolis
	Bittick, Wilbur H.	Minneapolis
‡	Blackard, Clyde E.	Minneapolis
‡	Blake, Allan J.	Hopkins
‡	Blake, James A.	Hopkins
‡	Blake, Paul S.	Minneapolis
	Bloch, Henry S.	Minneapolis
‡	Bloedel, Traugott J.	Osseo
‡	Blomberg, Robert D.	Minneapolis
‡	Bloom, David	Minneapolis
‡	Bloom, Norman B.	Minneapolis
‡	Blumenthal, Malcolm N.	Minneapolis
	Boardman, Peter J.	Minneapolis
‡	Boardman, William J.	Minneapolis
‡	Bofenkamp, Benjamin	Minneapolis
‡	Bohn, Donald G.	Minneapolis
†‡	Boies, Lawrence R., Sr.	Hopkins
	Bolt, Donald A.	Minneapolis
‡	Borman, Chauncey N.	Minneapolis
‡	Borowicz, Leonard A.	Minneapolis
	Bouthilet, Florence J.	Minneapolis
‡	Bowers, Gordon G.	Minnetonka
‡	Bowlin, Paul F.	Minneapolis
†	Boynton, Ruth E.	Miami, FL
	Bradley, Jeanne B.	Minneapolis
	Bradley, John G.	Minneapolis
‡	Brandt, Henry E.	Minneapolis
‡	Bransford, Paul W.	Minneapolis
‡	Brauer, William W.	Minneapolis
‡	Braun, Rene	Minneapolis
	Breitenbucher, Robert B.	Minneapolis
‡	Brekke, Harvey J.	Minneapolis
‡	Brennan, Joseph G.	Minneapolis
	Brill, Alice K.	Minneapolis
‡	Briones, Bienvenido R.	Hopkins
†	Brooks, Charles N.	Wayzata
‡	Brown, John H.	Minneapolis
	Brown, William D., Jr.	Minneapolis
‡	Buchstein, Harold F.	Minneapolis
‡	Buckley, Joseph J.	Minneapolis
‡	Bugby, Robert D.	Minneapolis
‡	Bugenstein, Robert H.	Minneapolis
‡	Buie, Louis A., Jr.	Minneapolis
‡	Bundt, Robert E.	Minneapolis
‡	Buran, David J.	Minneapolis
	Burchell, Howard B.	Minneapolis
‡	Burkholder, Dayton D.	Anoka
‡	Burnham, Wesley H.	Minneapolis
	Burton, Thomas P.	Minneapolis
‡	Cable, Morris L.	Minneapolis
‡	Cabot, Clyde M.	Minneapolis
	Calin, S. Hartley	Minneapolis
†	Cameron, Isabell L.	Minneapolis
‡	Campbell, Denis V.	Minneapolis
‡	Campbell, Orwood J.	Minneapolis
‡	Caplan, Leslie	Minneapolis
‡	Card, William H.	Minneapolis
	Cardle, James G.	Minneapolis
‡	Cardle, John B.	Minneapolis
	Carey, James B., Jr.	Minneapolis
‡	Carlander, Lester W.	Minneapolis
‡	Carlson, Charles V.	Mound
†	Carlson, Erik E.	Hopkins
‡	Carlson, Lawrence	Minneapolis
†‡	Caron, Robert P.	Minneapolis
‡	Carr, William J.	Minneapolis
	Carrier, Thomas C.	Minneapolis
‡	Caspers, Carl G.	Minneapolis
‡	Cauble, Charles F.	Minneapolis
†‡	Cavanor, Frank T.	Minneapolis
	Cavert, H. Mead	Minneapolis
‡	Ceder, Elmer T.	Minneapolis
‡	Cella, Joseph A.	Minneapolis
‡	Chadbourn, Wayne A.	Minneapolis
	Challman, S. Alan	Minneapolis
#‡	Chandler, William M.	Great Lakes, IL
‡	Chedister, Charles R.	Minneapolis
‡	Chesler, Merrill D.	Minneapolis
	Child, Sherman B.	Minneapolis
‡	Chisholm, Tague C.	Minneapolis
	Chou, Shelley N.	Minneapolis
‡	Christensen, Llewellyn E.	Minneapolis
	Christenson, Leland R.	Maple Plain
	Christgau, Roger A.	Minneapolis
	Clark, Malcolm D.	Minneapolis
‡	Clark, Robert S.	Minneapolis
‡	Clay, Lyman B.	Minneapolis
	Cline, David W.	Minneapolis
‡	Cochrane, Ray F.	Minneapolis
	Coe, John I.	Minneapolis
	Cohan, Richard C.	Minneapolis
‡	Cohen, Bernard A.	Minneapolis
	Cohen, Ephraim B.	Minneapolis
‡	Cohen, Henry W.	Wayzata
‡	Cohen, Sumner S.	Minneapolis
‡	Cole, James S.	Minneapolis
	Coleman, Thomas P.	Minneapolis
‡	Conlin, F. Dixon	Minneapolis
‡	Conlon, Daniel C.	Minneapolis
†	Connor, David G.	Minneapolis
‡	Cooper, John P.	Minneapolis
‡	Cooper, Robert R.	Minneapolis
†	Corniea, Albert D.	Minneapolis
‡	Correa, Dale H.	Minneapolis
	Corson, Wilfred A.	Minneapolis
‡	Cortez, Daniel P.	Minneapolis
‡	Coulter, Harold E.	Minneapolis
	Cowan, Donald W.	Minneapolis
	Craig, M. Elizabeth	Minneapolis
†‡	Cranmer, Richard R.	Laguna Hills, CA
	Cranston, Robert W.	Minneapolis
‡	Creevy, Charles D.	Minneapolis
‡	Crowley, Leonard V.	Minneapolis
†	Crutchfield, Susan E.	Fairchild AFB, WA
‡	Cullado, Andrionico F.	Minneapolis
	Culligan, Leo C.	Minneapolis
‡	Cundy, Donald T.	Minneapolis
	Curran, John P.	Anoka
	Cushing, Richard T.	Minneapolis
†	Cutts, George	Minneapolis
‡	Daggett, Donald R.	Minneapolis
†‡	Dahl, Elmer O.	Minneapolis
	Dahl, James C.	Minneapolis
†	Dahl, John A.	Minneapolis
†	Daniel, Donald H.	Minneapolis

Continued on Next Page

Hennepin County Medical Society *(Continued)*

‡	Danyluk, Michael	Minneapolis
	Dargay, Cyril P.	Minneapolis
‡	David, Reuben	Hopkins
†	Davis, Jay C.	Pompano Beach, FL
#‡	Davis, Michael W.	A.P.O. New York, NY
	Davis, Thomas H.	Minneapolis
	Dawson, Walter J., Jr.	Minneapolis
†	Dedeker, Kenneth L.	Minneapolis
	Delzell, Allen W.	Minneapolis
	Diamond, Robert A.	Minneapolis
	Dickman, Roy W.	Minneapolis
‡	Diefenbach, Eugene J.	Minneapolis
†	Diehl, Harold S.	New York, NY
	Diehl, James J.	Minneapolis
‡	Dierker, Heinrich A.	Minneapolis
†	Diessner, Henry D.	Minneapolis
‡	Doan, Robert E.	Wayzata
‡	Docherty, John A.	Minneapolis
‡	Donatelle, Edward P.	Minneapolis
†	Dorge, Richard	Minneapolis
	Dornbach, Robert A.	Minneapolis
‡	Dorsey, George C., Jr.	Minneapolis
‡	Dorsey, William E.	Minneapolis
	Doscherholmen, Alfred	Minneapolis
‡	Dougan, Jerome W.	Minneapolis
	DoVale, Joao M.	Edina
†	Doxey, Gilbert L.	Minneapolis
‡	Dredge, Thomas E., Sr.	Minneapolis
‡	Dredge, Thomas E., Jr.	Minneapolis
‡	Drill, Frederick E.	Minneapolis
‡	Drill, Herman E.	Hopkins
‡	Duff, Edwin R.	Minneapolis
	Duffy, John C.	Minneapolis
	Dummer, Donald J.	New Brighton
	Dumonceau, Roland G.	Minneapolis
	Duncan, Donald A.	Minneapolis
	Dunlap, David J.	Minneapolis
‡	Dunlap, Earl H.	Minneapolis
‡	Dupont, Joseph A.	Excelsior
	Duryea, Marbry	Minneapolis
‡	Duryea, Willis M.	Minneapolis
	Duryea, Willis M,, Jr.	Minneapolis
‡	Dvorak, Benjamin A.	Minneapolis
‡	Dwan, Paul F.	Minneapolis
†‡	Dworsky, Samuel D.	Minneapolis
	Earl, Stephan H.	Minneapolis
	Ebert, Richard V.	Minneapolis
	Eckerly, Jean R.	Minneapolis
‡	Eder, Walter P.	Minneapolis
‡	Edmondson, Hugh A., Jr.	Minneapolis
‡	Efteland, Myles E.	Minneapolis
†	Ehrenberg, Claude J.	Minneapolis
‡	Ehrlich, S. Paul	Minneapolis
	Eich, Matthew A.	Minneapolis
	Eichenlaub, John E.	Minneapolis
‡	Eichhorn, Edmund P., Jr.	Minneapolis
†	Eisenstadt, David H.	Minneapolis
‡	Eisenstadt, William S.	Minneapolis
	Eitel, George D.	Minneapolis
†	Ekdale, Robert A.	Menlo Park, CA
‡	Ellingson, Richard B.	Minneapolis
‡	Ellison, Evan S.	Minneapolis
	Elwood, Paul M., Jr.	Minneapolis
*†	Emond, Albert J.	Farmington
	Emond, Joseph S.	Farmington
	Emond, Joseph S., Jr.	Minneapolis
‡	Engel, Joseph P.	Minneapolis
‡	Englund, Elvin F.	Minneapolis
†	Engstrand, Oscar J.	Minneapolis
‡	Engstrom, E. Duane	Minneapolis
‡	Engwall, Richard L.	Minnetonka
‡	Erickson, Clifford O.	Minneapolis
‡	Erickson, Laurence F.	Minneapolis
‡	Erickson, Myron E.	Minneapolis
‡	Erickson, Reuben F.	Minneapolis
†	Ersek, Robert A.	Minneapolis
‡	Esensten, Sidney	Minneapolis
‡	Ettinger, Milton G.	Minneapolis
‡	Etzwiler, Donnell D.	Minneapolis
‡	Evans, Edward T.	Minneapolis
‡	Everhart, Clarence E., Jr.	Minneapolis
*†	Fahr, George E.	Minneapolis
†	Fallon, Virgil T.	Minneapolis
‡	Farber, Lawrence A.	Minneapolis
	Farley, Harrison H.	Minneapolis
	Farrell, T. Edwin	Minneapolis
†	Feeney, John M.	Excelsior
‡	Feigal, David W.	Wayzata
	Feinberg, Philip	Minneapolis
	Feinberg, Samuel B.	Minneapolis
†‡	Fenger, Ejvind P. K.	Chanhassen
‡	Fernandez, Rafael F., Jr.	Minneapolis
	Fetzek, Albert D.	Minneapolis
‡	Field, Charles W.	Minneapolis
	Fifer, Ellen Z.	St. Paul
	Fifer, William R.	Minneapolis
‡	Filiatrault, L. J.	Coon Rapids
‡	Filipovich, Orest N.	Minneapolis
‡	Fingerman, David L.	Minneapolis
‡	Fink, Leo W.	Minneapolis
‡	Fink, Robert J.	Minneapolis
†	Fink, Walter H.	Minneapolis
	Finlayson, Richard E.	Minneapolis
	Fischer, Albert P.	Wayzata
‡	Fisher, Don H.	Minneapolis
	Fisher, Isadore	Minneapolis
‡	Fleming, Dean S.	Minneapolis
‡	Fliehr, Richard R.	Minneapolis
	Flora, George C.	Minneapolis
‡	Florence, David W.	Minneapolis
	Flory, William D.	Minneapolis
	Foker, Leslie W.	Minneapolis
	Foley, Robert R.	Minneapolis
‡	Foley, William A.	Minneapolis
‡	Folsom, Louis B.	Minneapolis
‡	Forbes, Edward F.	Minneapolis
‡	Ford, W. Harold	Hopkins
‡	Foster, Orley W.	Minneapolis
‡	Fox, James Rogers	Minneapolis
‡	Frane, Donald B.	Minneapolis
‡	Frane, Gerald T.	Minneapolis
	Fredericks, George M.	Minneapolis
	Fredlund, Jon S.	Minneapolis
‡	Freeman, Craig W.	Minneapolis
	Freeman, Donald W.	St. Louis Park
‡	French, Lyle A.	Minneapolis
‡	Frey, Richard J.	Minneapolis
	Friberg, Joseph B.	Minneapolis
‡	Fried, Louis A.	Minneapolis
†‡	Friedell, Aaron	Minneapolis
	Friedell, George	Minneapolis
‡	Friedman, Harry S.	Minneapolis
‡	Friend, Charles A.	Minneapolis
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	Fruchtman, Stanley A.	Minneapolis
‡	Frykman, Howard M.	Minneapolis
‡	Frys, Russell N.	Minneapolis

Hennepin County Medical Society *(Continued)*

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	Fuglestad, J. Roald	Minneapolis
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†‡	Funk, Victor K.	Hopkins
	Furman, L. Christine	Minneapolis
	Fusaro, Ramon M.	Minneapolis
	Gaard, Richard C.	Robbinsdale
‡	Galbraith, Richard F.	Minneapolis
	Galejs, Aina	Minneapolis
‡	Gallett, Lester E.	Minneapolis
†	Galligan, Margaret Mary D.	Minneapolis
	Galway, Charles F.	Minneapolis
	Gamble, William G.	Minneapolis
‡	Gannon, Paul G.	Minneapolis
‡	Garamella, Joseph J.	Minneapolis
	Garetz, Floyd K.	Minneapolis
‡	Garske, George L.	Minneapolis
	Garten, Joseph L.	Minneapolis
‡	Garvey, James T.	Minneapolis
	Gault, Neal L., Jr.	San Francisco, CA
	Gasik, Joseph M.	Minneapolis
‡	Gaviser, David	Minneapolis
	Geller, Joseph	Minneapolis
‡	George, Vane P., Jr.	Le Sueur
	Gerster, Paul W.	Anoka
‡	Gibbs, Robert W.	Minneapolis
‡	Giebenhain, John N.	Minneapolis
‡	Giere, Joseph C.	Minneapolis
	Giere, Richard W.	Minneapolis
	Gilbert, Maurice G.	Minneapolis
	Gilbertsen, A. Sigrid	Minneapolis
	Gilbertsen, Victor A.	Minneapolis
#	Gilles, Paul J.	Great Lakes, IL
	Gingold, Benjamin A.	Minneapolis
	Glaeser, John H.	Minneapolis
‡	Godfrey, H. Wilson	Minneapolis
	Goehl, Reinhold O., Jr.	Minneapolis
	Gokcen, Barbara W.	Minneapolis
	Gokcen, Muharrem	Minneapolis
	Gold, David	Minneapolis
‡	Goldberg, Isadore M.	Minneapolis
	Goldberg, Marvin E.	Minneapolis
‡	Goldberg, Stanley M.	Minneapolis
	Goldfarb, Benjie L.	Minneapolis
	Goldfarb, Mace G.	Minneapolis
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‡	Goldner, Meyer Z.	Minneapolis
	Goldstein, Alan L.	Hopkins
‡	Good, Gary	Minneapolis
‡	Goodchild, William R.	Minneapolis
	Gordon, John R.	Minneapolis
	Gordon, Sewell S.	Minneapolis
	Gozum, Ekrem	Minneapolis
	Graham, John J.	Minneapolis
‡	Granquist, Richard D.	Minneapolis
	Grant, Suzanne	Minneapolis
†	Gratzek, Frank R.	Anoka
†	Gray, Royal C.	Minneapolis
†	Greden, John F.	Minneapolis
	Green, Clayton R.	Excelsior
	Green, Robert A.	Minneapolis
‡	Greenberg, Albert J.	Minneapolis
‡	Greene, Leonard H.	Minneapolis
‡	Greenfield, Irving	Minneapolis
	Greenwald, Stephen M.	Minneapolis
¶	Greisheimer, Esther M.	Philadelphia, PA
	Grimes, Marian	Minneapolis
‡	Grimmell, Francis J.	Minneapolis
‡	Grismer, Jerome T.	Minneapolis
†	Gronvall, Paul R.	Hopkins
	Grube, David W.	Minneapolis
#‡	Gruys, Robert I.	Chiayi, Taiwan
	Guerrero, Rafael A.	Minneapolis
	Guidote-Melich, Paz C.	New Brighton
	Gullickson, Glenn, Jr.	Minneapolis
‡	Gunlaugson, Frederick G.	Minneapolis
‡	Gustafson, Paul O.	Minneapolis
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	Gustilo, Ramon B.	Minneapolis
	Haas, John W.	Minneapolis
	Haberer, Helen R.	Minneapolis
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‡	Hagen, Kristofer	Minneapolis
‡	Hagen, Wayne S.	Minneapolis
	Haglin, John J.	Minneapolis
	Hakim, Ali A.	Minneapolis
	Hall, Arthur M.	Minneapolis
‡	Hall, Harry B.	Minneapolis
‡	Hall, Wendell H.	Minneapolis
‡	Hallin, Roger P.	Minneapolis
	Hambidge, Gove, Jr.	Minneapolis
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‡	Hamel, Joseph I.	Minneapolis
	Hammerstrom, Robert N.	Minneapolis
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*	Hannah, Hewitt B.	Minneapolis
‡	Hansen, Cyrus O.	Minneapolis
†‡	Hansen, Erling W.	Minnetonka
†	Hansen, Olga S.	Minneapolis
‡	Hansen, Rollin M.	Minneapolis
‡	Hanske, Edward A.	Minneapolis
†	Hanson, Harlow J.	Minneapolis
	Hanson, Harold B.	St. Paul
‡	Hanson, Harold W.	Minneapolis
†	Hanson, Henry V.	Green River, AZ
†‡	Hanson, Malcolm B.	Osseo
‡	Hanson, Mark C. L.	Minneapolis
	Hanson, Mildred S.	Minneapolis
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	Hanson, William B.	Minneapolis
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	Harris, Leon D.	Minneapolis
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	Hartman, Evelyn E.	Minneapolis
‡	Hartwig, John A.	Minneapolis
†‡	Harty, Jerome L.	Minneapolis
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‡	Hastings, Donald W.	Minneapolis
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‡	Hauser, Donald C.	Minneapolis
*†	Hauser, George W.	Seattle, WA
‡	Havel, Robert J.	Minneapolis
‡	Haven, Walter K.	Minneapolis
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‡	Hay, Lyle J.	Minneapolis
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‡	Haywa, E. William	Minneapolis
‡	Head, Douglas P.	Minneapolis

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	Herbert, Willis L.	Minneapolis
‡	Hess, Carroll N.	Minneapolis
‡	Heupel, Hermann W.	Minneapolis
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	Hiatt, John A.	Minneapolis
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‡	Hildebrandt, Walter C.	Minneapolis
‡	Hilgermann, George O.	Minneapolis
‡	Hill, Earl	Minneapolis
‡	Hill, Elmer M.	Minneapolis
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‡	Hitchcock, Claude R.	Minneapolis
‡	Hodges, Kenneth V.	Minneapolis
‡	Hoffert, Henry E.	Minneapolis
	Hoffman, Roy A.	Minneapolis
‡	Hoffman, Walter Lees	Minneapolis
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	Holm, Donald F.	Minneapolis
‡	Holmberg, Conrad J.	Minneapolis
‡	Holten, David R,	Minneapolis
	Holzapfel, Fred C.	Minneapolis
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‡	Hoppes, Emerson E.	Minneapolis
	Horecki, Henry	Minneapolis
	Horns, Howard L.	Minneapolis
‡	Horns, Norman	Minneapolis
‡	Horns, Richard C.	Minneapolis
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	House, James H.	Minneapolis
	Hovland, Melvin L.	Minneapolis
‡	Hovland, Richard D.	Minneapolis
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	Howard, Solomon E.	Minneapolis
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‡	Howell, John L.	Minneapolis
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‡	Huff, John S.	Minneapolis
‡	Hulteng, Donald B.	Minneapolis
*†	Hultkrans, Rudolph E.	Minneapolis
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‡	Hustad, Edward G.	Minneapolis
	Hymes, Alan C.	Minneapolis
†‡	Hymes, Charles	Minneapolis
	Ide, Arthur W., Jr.	Minneapolis
	Idstrom, Linneus G.	Minneapolis
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	Ingalls, Edgar G.	Minneapolis
‡	Iverslie, Philip C.	Minneapolis
	Iverson, Eleanor B.	Minneapolis
‡	Iverson, Rolf M.	Minneapolis
‡	Jackson, J. Albert	Minneapolis
	Jackson, Richard L.	Minneapolis
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‡	Jacobson, Loren J.	Minneapolis
	Jacobson, Wyman E.	St. Louis Park
‡	Jaffe, Manuel O.	Minneapolis
‡	Janda, George W., Jr.	Minneapolis
‡	Jay, Alan R.	Temple, TX
‡	Jefferies, William L.	Minneapolis
‡	Jensen, Nathan K.	Minneapolis
	Jensen, Paul A.	Minneapolis
	Jensen, Reynold A.	Minnetonka
‡	Jepson, William W.	Minneapolis
	Jerome, Bourne	Minneapolis
	Jerome, Elizabeth B. K.	Minneapolis
‡	Jeub, Robert P.	Minneapolis
‡	Jinkins, Roger E.	Excelsior
†	Johanson, Waldemar G., Jr.	Dallas, TX
‡	Johnson, Angelo G.	Minneapolis
‡	Johnson, Arthur B.	Minneapolis
	Johnson, Bradley D.	Minneapolis
‡	Johnson, David R.	Minneapolis
#‡	Johnson, Donald A.	Minneapolis
	Johnson, Edward A.	Minneapolis
‡	Johnson, Frank E.	Minneapolis
‡	Johnson, Gordon E.	Minneapolis
‡	Johnson, Harry A., Jr.	Minneapolis
†‡	Johnson, James A.	Minneapolis
‡	Johnson, John W.	Minneapolis
	Johnson, Norman P.	Minneapolis
	Johnson, Norman Paul	St. Paul
‡	Johnson, Norton T.	Minneapolis
	Johnson, Paul E.	Wayzata
‡	Johnson, Reinald G.	Minneapolis
†	Johnson, Reuben A.	Minneapolis
‡	Johnson, Richard S.	Minneapolis
‡	Johnson, Robert E.	Minneapolis
	Johnson, Thomas H., Jr.	Minneapolis
	Johnson, Youbert T.	Minneapolis
	Johnston, Donald K.	Minneapolis
	Jones, David G.	Minneapolis
†‡	Jones, Herbert W., Jr.	Minneapolis
‡	Jones, Richard H.	Minneapolis
	Jordan, Donald V.	Minneapolis
	Jorgensen, Harlan	Minneapolis
‡	Judd, Allen S.	Minneapolis
‡	Judd, Walter H.	Washington, DC
	Jurdy, Mitchell J.	Minneapolis
‡	Kadesky, Harold B.	Minneapolis
	Kaiser, Harold B.	Minneapolis
	Kalb, Thomas J.	Minneapolis
‡	Kallestad, Leonard L.	Wayzata
‡	Kane, Dennis J.	Minneapolis
‡	Kane, Morton C.	Minneapolis
‡	Kane, William J.	Minneapolis
‡	Kaplan, Arnold P.	Minneapolis
‡	Kaplan, Harold A.	Minneapolis
‡	Kaplan, J. Jacob	Minneapolis
‡	Karleen, Conrad I.	Minneapolis
‡	Karlen, Markle	Minneapolis
‡	Kasper, Robert E.	Excelsior
‡	Katkov, Harold	Wayzata
‡	Kaye, Dale R.	Minneapolis
	Katz, Beni	Minneapolis
	Kegel, James F.	Minneapolis
†‡	Kelby, Gjert M.	Minneapolis
‡	Kelly, Charles F.	Minneapolis
‡	Kelly, John C.	Minneapolis
‡	Kelly, John P.	Minneapolis
‡	Kelly, John T.	Minneapolis
	Kelly, William D.	Minneapolis
	Kennedy, Byrl J.	Minneapolis
†	Kennedy, Claude C.	Minneapolis
	Kennedy, William R,	Minneapolis
‡	Khorsand, Darius	Minneapolis
†‡	Kieffer, Stephen A.	Minneapolis
	Kim, Mark K.	Minneapolis
‡	Kimmel, George C.	Minneapolis

Hennepin County Medical Society *(Continued)*

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†	King, Frances W.	Minnetonka
†‡	Kinsella, Thomas J.	Minneapolis
‡	Kiser, Joseph C.	Minneapolis
	Kitchen, Clyde K.	Minneapolis
‡	Kjellsen, Douglas L.	Minneapolis
‡	Klassen, Arthur C.	Minneapolis
	Kleven, Lowell H.	Minneapolis
‡	Knapp, Miland E.	Minneapolis
†‡	Knight, Ralph T.	Minneapolis
†	Knight, Ray R.	Minneapolis
‡	Knobloch, William H.	Minneapolis
	Knudsen, Helen L.	Minneapolis
†	Koch, Michael F.	Minneapolis
	Kohlhase, Robert E.	Minneapolis
‡	Kolars, Charles P.	Minneapolis
†	Koller, Hermann M.	Minneapolis
†	Koller, Louis R.	Minneapolis
‡	Koller, Robert L.	Minneapolis
#	Kollmorgan, Rodger C.	APO, San Francisco, CA
	Koontz, Peter S.	Minneapolis
	Koos, Gerald W.	Minneapolis
	Korchik, John P.	Minneapolis
‡	Koropchak, Nickolas	Minneapolis
‡	Kostich, Nikola D.	Minneapolis
	Kottke, Frederic J.	Minneapolis
†	Koucky, Rudolph W.	Sagle, ID
‡	Kovack, Freeman D.	Minneapolis
‡	Kozak, Michael J.	Minneapolis
‡	Krafft, Walter E.	Minneapolis
‡	Kragh, Lyle V.	Minneapolis
	Kramer, Daniel W.	Minneapolis
‡	Kremen, Arnold J.	Minneapolis
	Krieser, Albert E.	Minneapolis
	Krystosek, Lee A.	Minneapolis
†‡	Kucera, Frank J.	Hopkins
†	Kucera, William J.	Santa Barbara, CA
‡	Kump, Warren L.	Minneapolis
‡	Kusz, Clarence V.	Minneapolis
‡	Kyllo, John E.	Minneapolis
	LaBree, John W.	Minneapolis
‡	Lagaard, Sheldon M.	Minneapolis
†	Lajoie, John M.	Minneapolis
‡	Lamb, H. Douglas	Minneapolis
‡	Lang, Leonard A.	Minneapolis
‡	Langer, Leonard O., Jr.	Minneapolis
‡	Lannon, James B.	Minneapolis
†‡	Lapierre, Arthur P.	Minneapolis
‡	Larsen, Frank W.	Minneapolis
	Larson, Arthur K.	Minneapolis
‡	Larson, Donald M.	Minneapolis
‡	Larson, Ernest J., Jr.	Minneapolis
	Larson, F. Wilmer	Minneapolis
‡	Larson, Lawrence M.	Minneapolis
*†	Larson, Leonard M.	Minneapolis
	Larson, Loren J.	Minneapolis
‡	Larson, Paul N.	Minneapolis
‡	Larson, Richard E.	Minneapolis
‡	Larson, Roger C.	Minneapolis
	Larson, Wyllis G.	Minneapolis
	Latts, Elliot M.	Minneapolis
†	LaVake, Rae T.	Minneapolis
	Lawrence, Van S.	Minneapolis
	Lawrow, John W.	Minneapolis
	Lawson, Warren R.	Minneapolis
‡	Lawton, James J., Jr.	Minneapolis
	Laymon, Carl W.	Minneapolis
†	Leach, Clifford G.	Burnsville

	Leavenworth, Richard O., Jr.	Minneapolis
‡	Leemhuis, Andrew J.	Minneapolis
	Lees, David C.	Minneapolis
‡	Leiferman, Robert J.	Minneapolis
	Leighton, John S.	Minneapolis
	Leinonen, Wendla E.	Anoka
‡	Lenz, Bernard W.	Minneapolis
‡	Lenz, Oa	Minneapolis
*†‡	Leonard, Lawrence J.	Minneapolis
‡	Leonard, Samuel	Minneapolis
	Lerner, A. Ross	Minneapolis
‡	Leslie, Loren R.	Minneapolis
‡	Leslie, W. Robert	Minneapolis
	Letson, Robert D.	Minneapolis
	Lester, Theodore H.	Minneapolis
‡	Levine, Howard M.	Minneapolis
†	Levitan, Alexander A.	Minneapolis
	Lewis, F. Bruce	Minneapolis
	Lewis, Glenn M., Jr.	Minneapolis
‡	Lick, Louis C.	Minneapolis
	Liebhaber, Henia F.	Anoka
‡	Lillehei, Richard C.	Minneapolis
‡	Limbeck, Donald A.	Minneapolis
†	Lindall, Arnold W., Jr.	Marine-on-St. Croix
‡	Lindberg, Vernon L.	Minneapolis
‡	Lindberg, Winston R.	Minneapolis
‡	Lindeland, Arthur T.	Minneapolis
‡	Lindemann, Charles E.	Minneapolis
‡	Linderholm, Bruce E.	Minneapolis
‡	Lindgren, Russell C.	Minneapolis
†‡	Lindquist, Richard H.	Minneapolis
‡	Lindseth, Esten O.	Minneapolis
‡	Linner, John H.	Minneapolis
‡	Linner, Paul W.	Minneapolis
	Lipschultz, Oscar	St. Louis Park
	Litman, Abraham B,	Minneapolis
†‡	Litman, Thomas	Minneapolis
	Lober, Paul H.	Minneapolis
	Locke, Murray S.	Minneapolis
	Lofsness, Stanley V.	Minneapolis
‡	Logothetis, John A.	Minneapolis
	Loken, Merle K.	Minneapolis
‡	Lott, Frederick H.	Minneapolis
†	Lovett, Beatrice R.	Minnetonka
	Lowe, Douglass A.	Minneapolis
	Lowry, Elizabeth C.	Minneapolis
	Lowry, Jeanette K.	Minneapolis
	Lowry, Paul T.	Minneapolis
*	Lowry, Thomas	Minneapolis
‡	Luckey, William T.	Minneapolis
	Lueck, Wallace W.	Minneapolis
‡	Lufkin, Nathaniel H.	Minneapolis
‡	Luh, Edwin F.	St. Paul
	Lund, George W.	Minneapolis
	Lund, Nancy R.	Minneapolis
‡	Lund, Richard R.	Minneapolis
†	Lundberg, Ruth I.	St. Paul
‡	Lundblad, Rodger R.	Minneapolis
†	Lundblad, Roy A.	Minneapolis
	Lundblad, Stanley W.	Minneapolis
†	Lundeberg, Karl R.	Minneapolis
	Lundquist, Charles B.	Minneapolis
‡	Lundquist, Virgil J. P.	Minneapolis
‡	Lynch, Michael F.	Minneapolis
	Lyon, Fred A.	Minneapolis
‡	Lyon, John D.	Hopkins
†‡	Lysne, Henry	Minneapolis

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Hennepin County Medical Society *(Continued)*

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‡	Lysyj, Anatol	Minneapolis
	Lyzenga, Anton G.	Minneapolis
	McCaffrey, F. John	Minneapolis
‡	McCampbell, Malcolm D.	Minneapolis
‡	McCannel, Malcolm A.	Minneapolis
†‡	McCarthy, Donald	Minneapolis
	McCollister, Robert J.	Minneapolis
‡	McCormick, Donald P.	Minneapolis
†	McDaniel, Orianna	Minneapolis
‡	McFarland, Arthur H.	Minneapolis
	McGandy, Robert F.	Minneapolis
†‡	McInerny, Maurice W.	Minneapolis
†	McKelvey, John M.	Minneapolis
‡	McKenna, James L.	Minneapolis
‡	McKenzie, Charles H.	Minneapolis
†‡	McKinlay, Chauncey A.	Minneapolis
	McKinlay, Gordon L.	Minneapolis
	McKinley, C. Richard	Minneapolis
†	McKinney, Frank S.	Minneapolis
	McLaughlin, Byron H.	Minneapolis
‡	McMahon, John E.	Minneapolis
‡	McMurtrie, William B.	Minneapolis
	McNeil, John J.	Minneapolis
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†‡	McPheeters, Herman O.	Minneapolis
†	MacDonald, Daniel A.	Minneapolis
	MacGibbon, James D.	Minneapolis
‡	MacKinnon, Donald C.	Minneapolis
†‡	Mach, Frank B.	Minneapolis
‡	Mach, John R.	Minneapolis
	Macheledt, Neil L.	Anoka
‡	Madsen, Donald O.	Minneapolis
‡	Maeder, Edward C.	Minneapolis
†	Maeder, Edward C., Jr.	St. Paul
‡	Magee, Timothy M.	Minneapolis
	Magraw, Richard M.	Garrett Park, MD
	Mahle, James P.	Minneapolis
†	Maland, Clarence O.	Minneapolis
‡	Malmquist, Carl P.	Minneapolis
	Mandel, Sheldon L.	Minneapolis
	Manick, Kenneth P.	Minneapolis
‡	Mankey, James C.	Minneapolis
	Mann, George A.	Minneapolis
‡	Manoles, Elias N.	Minneapolis
	Manolis, Deane C.	Minneapolis
‡	Mark, Aaron L.	Minneapolis
	Mark, Merle S.	Minneapolis
	Mark, Peter M.	Minneapolis
‡	Marking, George H.	Minneapolis
	Markland, Colin	Minneapolis
	Markovitz, Jack M.	Minneapolis
‡	Marte, Egon	Minneapolis
‡	Martin, Frank E.	Minneapolis
‡	Martin, George R.	Minneapolis
	Martinson, Carl J.	Wayzata
	Martinson, Elmer J.	Wayzata
‡	Maslansky, Robert A.	Minneapolis
	Massee, Joseph S.	Minneapolis
‡	Mattson, Hamlin A. N.	Minneapolis
	Maunder, John B.	Minneapolis
†	Maxeiner, Stanley R.	Minneapolis
‡	Maxeiner, S. R., Jr.	Minneapolis
‡	Mayberg, Donald M.	Minneapolis
	Meany, Thomas J.	Minneapolis
‡	Mecklenburg, Fred E.	Minneapolis
‡	Meeker, Henry C.	Minneapolis
	Meekin, Patrick C.	Minneapolis
	Melichar, Paul J.	Minneapolis
‡	Meller, Robert L.	Minneapolis
‡	Mensheha, Nicholas M.	Minneapolis
†	Menter, Robert R.	Edina
†	Merkel, Frederick K.	Minneapolis
‡	Merner, Thomas B.	Minneapolis
†	Merrick, Charlotte T.	St. Paul
	Messenheimer, Myron G.	Minneapolis
‡	Metz, Donald D.	Minneapolis
‡	Meyer, Alvin J.	Minneapolis
*†	Meyer, E. Lawrence	Winona
†	Michael, Joseph C.	Minneapolis
†‡	Michel, Henry H.	Minneapolis
†	Michelson, Henry E.	Minneapolis
†	Mickelson, Emma F. (Fronk)	Minneapolis
	Middlebrook, John E.	Minneapolis
†‡	Miller, Charles H., III	Minneapolis
†	Miller, Gerald J.	Minneapolis
‡	Miller, H. Dawes	Minneapolis
‡	Miller, Harold E.	Minneapolis
‡	Miller, Hugo E.	Minneapolis
‡	Miller, J. Carleton	Minneapolis
	Miller, William P.	Minneapolis
‡	Millett, D. Keith	Minneapolis
‡	Milton, John S.	Minneapolis
‡	Minder, John G.	Minneapolis
	Mindrum, Gerald G.	Minneapolis
	Minsky, Armen A.	Minneapolis
‡	Mitby, Irvin L.	Minneapolis
‡	Mitchell, Berton D.	Minneapolis
	Mitchell, Edward C.	Minneapolis
#	Mitchell, John S.	Seoul, Korea
‡	Mitchell, Mancel T.	Minneapolis
‡	Mixer, Harry W.	Minneapolis
‡	Moe, John H.	Minneapolis
†	Moe, W. Wyatt	Minneapolis
‡	Moehn, John T.	Minneapolis
	Moen, Johannes K.	Minneapolis
	Moghaddam, Alaeddin	Minneapolis
	Mollers, Theodore P.	Ft. Snelling
‡	Monson, Einer M.	Minneapolis
	Monson, Warren A.	Minneapolis
‡	Moody, David L.	Minneapolis
†	Moore, Irvin H.	Hopkins
	Moorhead, Marie	Minneapolis
‡	Moos, Daniel J.	Minneapolis
‡	Moral, Harvey M.	Minneapolis
	Moran, Leo J.	New Brighton
	Moriarty, James A.	Minneapolis
	Moriarty, Joseph D.	Coon Rapids
‡	Mork, A. Harold	Anoka
‡	Mork, Frank E.	Anoka
‡	Mork, Frank E., Jr.	Minneapolis
	Morrison, Charlotte J.	Minneapolis
	Moss, Nyel H.	Minneapolis
‡	Mosser, Donn G.	Minneapolis
‡	Moyer, Leonard B.	Minneapolis
‡	Mulholland, William M.	Minneapolis
‡	Mullin, Gerald T., Jr.	Minneapolis
‡	Mulvahill, John E.	Minneapolis
‡	Munkittrick, Ronald C.	Minneapolis
	Murray, Elisabeth M.	Minneapolis
‡	Muske, Marvin M.	Minneapolis
‡	Musty, Nicholas J.	Minneapolis
	Myers, Jay A.	Minneapolis
	Myers, Thomas T., III	Minneapolis
‡	Myhre, James	Minneapolis
	Mylrea, Murray J.	Burnsville

Hennepin County Medical Society *(Continued)*

‡	Nagobads, Ilgvars J.	Minneapolis
	Nagobads, V. George	Minneapolis
‡	Najarian, John S.	Minneapolis
	Nash, Eldore B.	Minneapolis
†‡	Neal, Joe M.	Minneapolis
‡	Neary, Richard P.	Minneapolis
†	Nelson, Bernice A.	Minneapolis
	Nelson, C. Barton	Minneapolis
	Nelson, Carleton A.	Minneapolis
†‡	Nelson, David J.	Minneapolis
‡	Nelson, Edward N.	Minneapolis
‡	Nelson, George E.	Minneapolis
‡	Nelson, Gunard A.	Minneapolis
†‡	Nelson, Harvey	Minneapolis
‡	Nelson, Lloyd S.	Minneapolis
	Nelson, Maxine O.	Minneapolis
‡	Nelson, Maynard C.	Minneapolis
‡	Nelson, O. L. Norman	Minneapolis
‡	Nelson, Wallace I.	Minneapolis
	Nerenberg, Sidney	Minneapolis
‡	Nesset, Lawren B.	Minneapolis
‡	Nesset, William D.	Minneapolis
	Neumann, Roland F.	Minneapolis
‡	Neumeister, Charles A.	Minneapolis
	Neuwirth, Gerardo D.	Golden Valley
	Nicholas, S. Scott, Jr.	Minneapolis
#	Nielsen, David J.	Minneapolis
‡	Nilsen, John A.	Minneapolis
	Nolan, Robert K.	Brooklyn Center
‡	Noran, Harold H.	Minneapolis
‡	Nord, Robert E.	Minneapolis
†	Nordin, Gustaf T.	Kaneohe, HI
‡	Norman, Franklin C.	Minneapolis
‡	Norman, Mark L., Jr.	Minneapolis
	Norval, Mildred A.	Minneapolis
	Nuessle, William F.	Minneapolis
	Nydahl, Bruce C.	Minneapolis
‡	Nydahl, Malvin J.	Minneapolis
	O'Brien, Bruce J.	Minneapolis
‡	O'Brien, William A.	Minneapolis
†	O'Donnell, James E.	Minneapolis
	O'Neil, Bernerd L.	Minneapolis
‡	O'Phelan, E. Harvey	Minneapolis
	Officer, Charles D.	Burnsville
	Olavs, Olga	Minneapolis
‡	Olfelt, Paul C.	Minneapolis
†‡	Olsen, E. George	Minnetonka
‡	Olsen, Jay R.	Minneapolis
‡	Olson, Alton C.	Minneapolis
‡	Olson, C. Kent	Minneapolis
	Olson, Carl J.	Minneapolis
‡	Olson, Detlof M.	Minneapolis
‡	Olson, Duane C.	Minneapolis
	Olson, Hardin E.	Minneapolis
†	Olson, Olof A.	Minneapolis
‡	Olson, Philip A.	Minneapolis
‡	Olson, Robert A.	Minneapolis
	Olson, Robert E.	Minneapolis
	Olson, Robert W.	Minneapolis
	Olson, Rolland A.	Wayzata
#	Onstad, Gerald R.	Fort Rucker, AL
‡	Opheim, Richard H.	Minneapolis
‡	Oppen, E. Gerhard	Minneapolis
‡	Oppen, Melvin G.	Minnetonka
	Opstad, Earl T.	Minneapolis
‡	Orbuch, Martin W.	Minneapolis
‡	Orkin, Milton	Minneapolis
	Orn, Duane L.	Minneapolis
	Osterberg, Kenneth A.	Minneapolis
	Ott, Eugene C.	Minneapolis
†	Overby, Philip G.	Minneapolis
	Owen, Richard R.	Minneapolis
	Paal, Dwain J.	Minneapolis
†	Page, Raymond L.	Minneapolis
	Paisner, Hyman M.	Minneapolis
‡	Palen, Benjamin J.	Scottsdale, AZ
‡	Palm, E. Theodore	Minneapolis
	Paparella, Michael M.	Minneapolis
	Papermaster, Ralph	Minneapolis
‡	Papermaster, Theodore C.	Wayzata
	Park, Wilford E.	Minneapolis
	Parod, John D.	Minneapolis
‡	Parrott, John C.	Minneapolis
‡	Pattee, James J.	Minneapolis
‡	Patterson, Paul G.	Minneapolis
	Paule, William J.	Minneapolis
	Peake, Janna Z.	Minneapolis
‡	Peiper, Warren S.	Minneapolis
‡	Peluso, Charles R.	Minneapolis
	Pennington, Mary	Minneapolis
‡	Peper, Martin C.	Minneapolis
‡	Perlman, Everett C.	Minneapolis
	Perlman, Herschel L.	St. Louis Park
‡	Peteler, Jennings C. L.	Minneapolis
	Petersen, Byron D.	Minneapolis
‡	Petersen, Deane A.	Wayzata
‡	Petersen, Glenn L.	Minneapolis
‡	Petersen, William E.	Minneapolis
‡	Peterson, Charles A.	Minneapolis
	Peterson, Charles R.	Minneapolis
	Peterson, John A.	Minneapolis
‡	Peterson, Oliver H., Jr.	Minneapolis
	Peterson, Palmer A.	Minneapolis
‡	Peterson, Theodore A.	Minneapolis
*	Peterson, W. Henry	Minneapolis
†	Peterson, Willard C., Sr.	Minneapolis
‡	Peterson, Willard C., Jr.	Minneapolis
‡	Petit, Julien V.	Minneapolis
†‡	Petit, Leon J.	Minneapolis
‡	Pewters, John T.	Minneapolis
‡	Pfohl, Richard A.	Minneapolis
†	Phelps, Kenneth A.	St. Petersburg, FL
	Phelps, Robert D.	Minneapolis
	Phibbs, Clifford M., Jr.	Minneapolis
	Pilling, Loran F.	Minneapolis
	Pincus, Mitchell	Minneapolis
	Pizarro, Remi L.	Minneapolis
‡	Plasha, Matthew K.	Coon Rapids
‡	Plass, Herbert F. R.	Minneapolis
‡	Pleissner, Karl W.	Minneapolis
‡	Plimpton, Nathan C.	Minneapolis
	Pohl, John F.	Minneapolis
	Polesky, Herbert F.	Minneapolis
	Poley, Brooks J.	Minneapolis
‡	Pollak, Kurt	Minneapolis
‡	Pollock, Anthony J.	Edina
†‡	Polzak, Jacob A.	Minneapolis
	Pone, John J.	Minneapolis
‡	Popadiuk, Peter	Minneapolis
‡	Popowich, John G.	Minneapolis
†	Poppe, Frederick H.	Miami, FL
‡	Potter, Robert B.	Minneapolis
‡	Pratt, Fred J., Jr.	Minneapolis
‡	Prem, Konald A.	Minneapolis

Continued on Next Page

Hennepin County Medical Society *(Continued)*

‡	Preston, Frank S., Jr.	Minneapolis
‡	Price, William E.	Minneapolis
	Prickman, William E.	Minneapolis
‡	Priest, Robert E.	Minneapolis
†‡	Prim, Joseph A.	Minneapolis
‡	Proshek, Lumir C.	Minneapolis
‡	Quello, Robert O. B.	Minneapolis
	Quiggle, Arthur B.	Minneapolis
‡	Quist, Henry W., Jr	Minneapolis
‡	Raab, David E.	Minneapolis
	Racer, Harley J.	Minneapolis
	Raich, John J.	Minneapolis
‡	Raile, Richard B.	Minneapolis
	Randall, David A.	Minneapolis
‡	Ransom, H. Robert	Osseo
‡	Ratelle, Alexander E.	Minneapolis
	Recht, Thomas M.	Minneapolis
‡	Reece, Richard L.	Minneapolis
	Reed, Sheldon C.	Minneapolis
‡	Regan, John J.	Minneapolis
†‡	Regnier, Edward A.	Minneapolis
	Reichel, Samuel M.	Minneapolis
‡	Reif, Harold A.	Minneapolis
‡	Reiley, Richard E.	Minneapolis
	Reinhart, Richard O.	Minneapolis
‡	Reiser, Milton P.	Minneapolis
†	Reller, Carl Raymond, Jr.	Minneapolis
‡	Remole, William D.	Minneapolis
‡	Remsberg, John	Minneapolis
‡	Resch, Joseph A.	Minneapolis
‡	Reynolds, James	Minneapolis
‡	Rholl, Arnold O.	Minneapolis
‡	Rice, Carl O.	Minneapolis
	Rice, Edwin S.	Minneapolis
	Rice, Fred A.	Minneapolis
‡	Richardson, Robert J.	Minneapolis
†‡	Richdorf, Lawrence F.	Minneapolis
‡	Rieke, W. W.	Wayzata
	Rierson, Phillip A.	Minneapolis
	Riley, John D.	Minneapolis
	Riley, William J.	Minneapolis
	Riordan, Elsie M.	Minneapolis
‡	Ripple, Rudolph J., Jr.	Minneapolis
‡	Risch, Ronald E.	Minneapolis
‡	Rizer, Dean K.	Minneapolis
†	Robb, Edwin F.	Minneapolis
‡	Robbins, Owen F.	Minneapolis
	Roberts, Byron H.	Minneapolis
‡	Roberts, Lewis J.	Minneapolis
‡	Roberts, Stanley W.	Minneapolis
	Robinson, Cortland O.	Minneapolis
‡	Rock, William H.	Anoka
‡	Rocknem, Robert E.	Minneapolis
	Rockwell, Curtiss V.	Minneapolis
‡	Rodgers, Richard S.	Minneapolis
‡	Rogin, Norton	Minneapolis
‡	Rollins, Pat	Minnetonka
‡	Romness, Kenneth B.	Mound
‡	Rosenbaum, David L.	Minneapolis
‡	Rosendahl, Frederick G.	Minneapolis
†	Rosenfield, Abraham B.	Minneapolis
†	Rosenquist, Rudolph J.	Minneapolis
	Rosenstein, Hanan J.	Minneapolis
	Rosenow, John H.	Minneapolis
†‡	Rosenwald, Reuben M.	Anoka
‡	Rossen, Ralph	Minneapolis
‡	Rotenberg, Robert J.	Minneapolis
	Rotenberg, Samuel	Minneapolis
‡	Rothnem, Morris S.	Minneapolis
‡	Rubin, Manly	Minneapolis
	Rucker, Thomas K.	Minneapolis
†	Rucker, William H.	Minneapolis
†	Rud, Norman E.	Edina
	Runquist, Richard K.	Cambridge
‡	Russeth, Arthur N.	Minneapolis
‡	Rusten, Elmer M.	Minneapolis
	Rydberg, John S.	Minneapolis
	Rydburg, Wayne C.	Minneapolis
‡	Rydland, Arne D.	Minneapolis
‡	St. Cyr, Harry M.	Minneapolis
‡	St. Cyr, Kenneth J.	Minneapolis
‡	Saliterman, Bernard I.	Minneapolis
‡	Salovich, Edward L.	Minneapolis
‡	Salovich, Elmer R.	Minneapolis
‡	Sanchez, Jose S.	Edina
‡	Sandt, Karl E.	La Jolla, CA
‡	Sanfilippo, Sylvester J.	Minneapolis
	Sartor, Richard	Minneapolis
‡	Sayther, Keith D.	Minneapolis
‡	Sborov, Abe M.	Minneapolis
	Scallen, Raymond W.	Minneapolis
‡	Scanlan, Patrick J.	Minneapolis
	Schaar, Frances E.	Minneapolis
	Schaefer, Wesley G.	Minneapolis
	Schaffhausen, Irwin F.	Minneapolis
	Schaffhausen, Mildred	Minneapolis
‡	Scherer, L. Raymond	Minneapolis
	Scherling, Sidney S.	Minneapolis
	Schiele, Burtrum C.	Minneapolis
	Schissel, Gregory A.	Minneapolis
‡	Schmidt, W. Robert	Minneapolis
†	Schmitt, Samuel C.	Fallbrook, CA
	Schneck, Jack I.	Minneapolis
	Schoening, Herbert A.	Minneapolis
	Schoenwetter, William F.	Minneapolis
‡#	Schottler, Jerry L.	Minneapolis
	Schottler, Max E.	Minneapolis
†	Schroeder, Albert J.	Minneapolis
‡	Schultz, Alvin L.	Minneapolis
*	Schultz, Earl A.	Los Angeles, CA
‡	Schultz, J. Harold	Minneapolis
‡	Schultz, Peter J.	Minneapolis
	Schultz, Robert J.	Minneapolis
‡	Schulze, William M.	Minneapolis
	Schumacher, Robert V.	Minneapolis
‡	Schumacher, John W.	Minneapolis
	Schut, Lawrence J,	Minneapolis
	Schwartz, E. Robert	Minneapolis
‡	Scott, Horace G.	Minneapolis
	Scott, Robert H.	Minneapolis
†	Seaberg, John A.	Pequot Lakes
	Seay, James E., III	Minneapolis
‡	Segal, Edward L.	Minneapolis
‡	Segal, Martin A.	Minneapolis
	Segal, Marvin S.	Minneapolis
‡	Segal, Sheldon J.	Minneapolis
†	Seham, Max	St. Paul
	Seibel, David I.	Minneapolis
‡	Seifert, Milton H.	Excelsior
‡	Seifert, Milton H., Jr.	Excelsior
	Seljeskog, Edward L.	Minneapolis
	Semba, Thomas	Minneapolis
‡	Semsch, Robert D.	Wayzata
	Severseike, Odean M.	Minneapolis
‡	Shandorf, James F.	Minneapolis

Hennepin County Medical Society *(Continued)*

†	Shaperman, Eva P.	La Mesa, CA
	Shapiro, Irving	Minneapolis
	Shapiro, Sidney K.	Minneapolis
‡	Shapiro, Stanley W.	Minneapolis
‡	Shattuck, Clark A.	Minneapolis
‡	Shaw, Howard A.	Minneapolis
‡	Shea, Andrew W.	Minneapolis
	Shemesh, Alvin	Minneapolis
‡	Sher, Lewis	Minneapolis
‡	Sherman, Lloyd F.	Minneapolis
†	Shillington, Maurice A.	Ft. Lauderdale, FL
	Sholler, Lawrence J.	Minneapolis
‡	Shragg, Robert I.	Minneapolis
‡	Shronts, John F.	Minneapolis
	Sidell, Franklin D.	Minneapolis
	Siegmann, William C.	Minneapolis
‡	Sigel, Melvin E.	Minneapolis
‡	Silas, Ralph M.	Minneapolis
	Silver, John D.	Minneapolis
‡	Silverstein, Paul M.	Minneapolis
‡	Simmons, Richard K.	Minneapolis
	Simo, Kathleen Kay	Minneapolis
‡	Simonson, Donald B.	Minneapolis
†	Simpson, Ellery De W.	Phoenix, AZ
‡	Sinykin, Melvin B.	Minneapolis
	Sipe, James W.	Coon Rapids
‡	Skjold, Arthur C.	Minneapolis
	Slosser, Gaius J., II	Minneapolis
	Smiley, John T.	Minneapolis
†‡	Smisek,, Frank M.	Minneapolis
†	Smith, Adam M.	Minneapolis
‡	Smith, Archie M.	Minneapolis
	Smith, Barlow	Minneapolis
‡	Smith, Baxter A., Jr.	Minneapolis
‡	Smith, Graham G.	Minneapolis
	Smith, Henry T.	Minneapolis
‡	Smith, John E.	Minneapolis
	Smith, Nadine G.	Minneapolis
‡	Smith, Theodore S.	Minneapolis
‡	Soderlind, Ragnar T.	Minneapolis
‡	Soiseth, Robert P.	Minneapolis
‡	Solhaug, Samuel B., Jr	Minneapolis
‡	Solvason, Harold M.	Minneapolis
	Spain, W. Thomas	Evansville, IN
‡	Spano, Joseph P.	Minneapolis
‡	Spencer, Bernard J.	Minneapolis
‡	Spencer, David L.	Anoka
‡	Spink, Wesley W.	Minneapolis
‡	Sponsel, Kenath H.	Minneapolis
‡	Stahr, Aubrey C.	Hopkins
†	Stanford, Charles E.	Boynton Beach, FL
†	Stanley, Court R.	Minneapolis
‡	Staub, Henry P.	Minneapolis
‡	Steidl, Richard M.	Minneapolis
‡	Stelter, Lloyd A.	Minneapolis
†	Stenstrom, Annette T.	Holmes Beach, FL
	Stenzel, Donald A.	Minneapolis
	Stenzel, Joseph A.	Minneapolis
‡	Stephens, William E.	Minneapolis
	Sterrie, Norman A.	Minneapolis
†	Stewart, Marvin J.	Minneapolis
‡	Stewart, Paul B.	Minneapolis
‡	Stiegler, Farrell S.	Minneapolis
‡	Stoesser, Albert V.	Minneapolis
#	Stolee, Curtis N.	Ft. Dauphin, Madagascar
‡	Stoltz, Robert C.	Minneapolis
	Stone, Norman F.	Minneapolis
	Stone, Stanley P.	Minneapolis
‡	Strait, Herbert S.	Minneapolis
‡	Strand, Clarence M.	Minneapolis
‡	Streu, Richard E.	Minneapolis
	Strickland, Martha J. B.	Minneapolis
‡	Strickler, Jacob H.	Minneapolis
	Strobel, Jack L.	Minneapolis
‡	Strom, Gordon W.	Minneapolis
‡	Strom, Robert L.	Minneapolis
‡	Stromgren, Delph T.	Minneapolis
†	Stromme, William B.	Minneapolis
	Strunk, Clarence A.	Minneapolis
‡	Student, Richard E.	Minneapolis
‡	Sturges, Robert L.	Minneapolis
	Subak, Barbara H.	Minneapolis
‡	Subby, Walter	Minneapolis
	Sukov, Marvin	Minneapolis
‡	Sulciner, Aurel	Minnetonka
‡	Sundberg, A. Bruce	Minneapolis
	Swaiman, Kenneth F.	Minneapolis
‡	Swallen, Thomas O.	Minneapolis
†‡	Swanson, David A.	Minneapolis
	Swanson, John O.	Minneapolis
‡	Sweetser, Horatio B.	Minneapolis
‡	Sweetser, Theodore H., Jr.	Minneapolis
‡	Swendseen, Carl J.	Minneapolis
	Swenson, James D.	Minneapolis
‡	Swenson, Richard W.	Minneapolis
	Swift, Dean C.	Minneapolis
	Symchych, Boris E.	Minneapolis
‡	Tam, Ernest C.	Minneapolis
‡	Tambornino, Joseph M.	Minneapolis
‡	Tanaka, Shin	Minneapolis
‡	Tangen, George V.	Minneapolis
†	Taylor, Joseph H.	Ft. Lauderdale, FL
‡	Tchou, Mien-Fa	Minneapolis
‡	Tenner, Robert J.	Minneapolis
‡	Teska, Byron A.	Minneapolis
‡	Teynor, Joseph W.	Minneapolis
‡	Tharp, Ralph	Minneapolis
	Thelemann, Arthur R., Jr,	Minneapolis
	Theobalt, Inge M.	Minneapolis
	Theologides, Athanasios	Minneapolis
	Thomas, William H.	Minnetonka
‡	Thomasson, Robert D.	Minneapolis
	Thomes, A. Boyd	Minneapolis
	Thompson, Arthur	Minneapolis
‡	Thorson, Stuart V.	Minneapolis
‡	Thysell, Desmond M.	Minneapolis
‡	Titrud, Leonard A.	Minneapolis
‡	Tobin, John A.	Minneapolis
	Tobin, John D.	Minneapolis
	Thorp, William B.	Minneapolis
	Torres, Fernando	Minneapolis
†	Town, Louise A.	Edina
‡	Townes, C. Dwight, Jr.	Minneapolis
	Trach, Benedict B.	Minneapolis
	Treat, William A.	Minneapolis
‡	Trost, Francis J.	Minneapolis
‡	Trow, James E.	Minneapolis
	Trow, William H.	Hopkins
	Tsai, Shih Hao	Minnetonka
‡	Tucker, Richard C.	Minneapolis
‡	Tudor, Richard B.	Minneapolis
‡	Turkbas, Nejat	St. Paul
‡	Twidwell, Joseph E.	Minneapolis
‡	Ulvestad, Harold S.	Minneapolis

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Hennepin County Medical Society *(Continued)*

‡	Utendorfer, Robert W.	Minneapolis
	Vaaler, Robert T.	Minneapolis
‡	Valgemae, Romil	Minneapolis
#	Van Oppen, Dirk J. A.	Minneapolis
‡	Vellek, Donald G.	Minneapolis
	Vennes, Jack A.	Minneapolis
	Vik, A. Elliott	Minneapolis
‡	Von Drashek, Stanley C.	Minneapolis
	Vorlicky, Loren N.	Minneapolis
	Wagner, Christian J.	Minneapolis
‡	Wagner, Robert M.	Minneapolis
†	Waldron, Carl W.	Scottsdale, AZ
‡	Waldron, John F.	Minneapolis
‡	Wall, Carl R.	Minneapolis
	Wallinga, Jack V.	Minneapolis
†‡	Walonick, Albert L.	Hopkins
*	Walsh, Francis M.	Minneapolis
#	Walsh, John G.	Silver Spring, MD
	Wang, Yang	Minneapolis
†‡	Wangensteen, Owen H.	Minneapolis
‡	Warren, John W.	Minneapolis
‡	Watson, C. Gordon	Minneapolis
	Watson, Cecil J.	Minneapolis
	Wattenberg, Lee W.	Minneapolis
‡	Weatherhead, Donald S. P.	Minneapolis
‡	Webb, Edgar A.	Minneapolis
‡	Webber, Richard J.	Minneapolis
‡	Weber, Lowell W.	Minneapolis
‡	Weisberg, Rapheal J.	Minneapolis
	Weisel, Mary R.	Minneapolis
‡	Wendland, John P.	Minneapolis
	Werner, George	Minneapolis
‡	Wesolowski, Stanley	Minneapolis
†	West, Catherine C.	Edina
	Wester, Mary Sue	Minneapolis
‡	Westgate, Hugh D.	Minneapolis
	Wetherby, Macnider	Minneapolis
	Wethington, Joseph F.	Coon Rapids
‡	Wett, Richard J.	Minneapolis
	Wexler, Harold M.	Minneapolis
‡	Wheeler, Robert W.	Minneapolis
	Whitacre, John C., II	Minneapolis
	White, Asher A.	Minneapolis
†	White, Willard D.	Minneapolis
‡	Whitesell, Lloyd A.	Minneapolis
‡	Widen, Wilford F.	Minneapolis
‡	Wigdahl, Luther O.	Minneapolis
‡	Wilcox, William A.	Minneapolis
	Wild, John J.	Minneapolis
†	Wilder, Kenneth W.	Minneapolis
†	Wilder, Robert L.	Minneapolis
†	Wilder, Russell M., Jr.	Topeka, KS
‡	Wilder, Walter L.	Minneapolis
‡	Wilken, Paul A.	Minneapolis
‡	Williams, Henry L.	Minneapolis
‡	Williams, Paul A.	Minneapolis
‡	Williams, Richard E.	Robbinsdale
‡	Wilson, John A.	Minneapolis
‡	Wilson, Robert E.	Minneapolis
‡	Wilson, Thomas M., Jr.	Minneapolis
	Winchell, Paul	Minneapolis
†	Winther, Nora M. C.	Columbus, OH
‡	Wippermann, Frederic F.	Minneapolis
‡	Wisiol, Erich S.	Minneapolis
‡	Wisness, Osmund A.	Savage
	Woellner, Richard C.	Minneapolis
†‡	Wohlrabe, Arthur A.	Minneapolis
‡	Wohlrabe, A. Cabot	Minneapolis
‡	Wohlrabe, Robert G.	Minneapolis
‡	Wolter, Fred H.	Minneapolis
	Woodley, Donald W.	Minneapolis
‡	Worrell, Philip J.	Minneapolis
‡	Woyda, William C.	Minneapolis
	Wright, Donald L.	Minneapolis
‡	Wright, Francis S.	Minneapolis
	Wright, William S.	Minneapolis
	Wuest, Frederick C.	Wayzata
†	Wynne, Herbert M. N.	Minneapolis
‡	Yeager, Terrell F.	Anoka
‡	Yelle, Matthew D.	Anoka
‡	Ylvisaker, Ragnvald S.	Minneapolis
	Yonehiro, Earl G.	Minneapolis
	Young, Ronald C.	Minneapolis
†	Yue, Wen Y.	Minneapolis
	Zahrendt, O. Lewis	Minneapolis
	Zak, Solomon J.	Minneapolis
‡	Zarling, V. Richard	Minneapolis
‡	Zaworski, Leo A.	Minneapolis
‡	Zelickson, Alvin S.	Minneapolis
#†	Zemmers, Robert M.	Spanaway, WA
	Zierold, Arthur A.	Minneapolis
	Zimmerman, Donald E.	Minneapolis
‡	Zinn, Charles W.	Wayzata
‡	Zinter, Ferdinand A.	Minneapolis

KANDIYOHI-SWIFT-MEEKER COUNTY MEDICAL SOCIETY

Kandiyohi, Swift and Meeker Counties
Regular meetings, third Thursday of each month
Annual meeting in November
Number of members 59

PRESIDENT

Nolen, William A. . . . . . Willmar

SECRETARY

Leitch, Cecil M. . . . . . Litchfield

‡	Allison, David D.	Litchfield
†	Anderson, Richard E.	Willmar
‡	Bosland, Howard G.	Willmar
	Chunn, Stanley S.	Willmar
	Danielson, Lennox	Litchfield
‡	Dille, Donald E.	Litchfield
‡	Docksey, John W.	Willmar
	Dreyling, Roger A.	Eden Valley
	Dunstan, Paul L.	Willmar
	Eberley, Tobe S.	Benson
	Eichelberger, Dale L.	Willmar
‡	Ellinger, Albert J.	Willmar
	Fedor, Robert D.	Litchfield
†	Frederickson, Alice C.	Willmar
	Gaebe, Milton B.	Clara City
†	Giere, Silas W.	Benson
	Griffin, Richard P.	Benson
‡	Guy, Jack A.	New London
	Hazen, Richard W.	Willmar
‡	Hinderaker, Harris P.	Willmar
‡	Hinz, Walter E.	Willmar
‡	Hodapp, Robert V.	Willmar

Kandiyohi—Swift—Meeker County Medical Society
(Continued)

Houts, Joseph C. .... Dassel
Jacobs, Douglas L. .... Willmar
Johnson, Daniel A. .... Litchfield
‡ Johnson, Marvin W. .... Dassel
‡ Kaufman, Edward J. .... Appleton
Kvale, James N. .... Atwater
Larrabee, Walter F., Jr. .... Willmar
Leitch, Cecil M. .... Litchfield
McAfee, David K. .... Willmar
McCarthy, Austin M. .... Willmar
Macklin, William E. .... Litchfield
Mattson, Donald S. .... Willmar
‡ Meinert, John K. .... Willmar
‡ Michels, Roger P. .... Willmar
‡ Munneke, Lyle .... Clara City
‡ Nelson, Robert H. .... Benson
Nolen, William A. .... Litchfield
‡ Olson, Gregory M. .... Litchfield
‡ Opsahl, Lawrence J. .... Willmar
Petersen, Donald H. .... Willmar
‡ Peterson, Willard .... Willmar
‡ Proeschel, Ray K. .... Willmar
Reid, William O. .... Willmar
#‡Robinson, William W. .... Agana, Guam
‡ Rorem, Joseph A. .... Appleton
‡ Ruchie, Warren H. .... Willmar
‡ Ruhe, Albert .... Willmar
Rygh, Harold N. .... Atwater
Salter, William M. .... Willmar
Schnell, Frederick S. .... Litchfield
Skaife, William F. .... Benson
Smith, Lloyd A. .... Willmar
†‡ Solsem, Frederick N. S. .... Spicer
‡ Thompson, Russell A. .... Willmar
‡ Wagner, Norman W. .... Benson
Wilmot, Cecil A. .... Litchfield
† Wilmot, Harold E. .... Litchfield

LYON-LINCOLN COUNTY MEDICAL SOCIETY

Lyon and Lincoln Counties
Regular meetings, 6 meetings—Spring and Fall
Annual meeting, winter quarter
Number of members 23

PRESIDENT
Bosley, Patrick .... Balaton

SECRETARY
Boyum, Allan J. .... Marshall

Bosley, Patrick .... Balaton
‡ Boyum, Allan J. .... Marshall
‡ Eckdale, John E. .... Marshall
† Ford, Burton C. .... Marshall
‡ Hedenstrom, Philip C. .... Marshall
‡ Johnson, C. Percy .... Tyler
# Johnston, Bemis H. .... Eatontown, NJ
† Kreuzer, Titus C. .... Ft. Snelling
Lee, Norman J. .... Tracy
‡ Monson, Leonard J. .... Canby
‡ Mueller, LeRoy E. .... Hendricks
‡ Muesing, Mark A. .... Tyler
‡ Murphy, Joseph E. .... Marshall
‡ Myers, John W. .... Canby
‡ Olson, Robert T. .... Canby
‡ Peterson, Kenneth A. .... Marshall
† Rohrer, Christian A. .... Madison Lake
Stover, Laddie E. .... Marshall
#‡Sutherland, John E. .... Indian Head, MD
‡ Taintor, Ronald W. .... Marshall
‡ Thompson, Carl O. .... Hendricks
† Workman, Warner G. .... Tracy
† Yaeger, Wilbert W. .... Torrance, CA

McLEOD COUNTY MEDICAL SOCIETY

McLeod County
Regular meetings, third Thursday of each month
Annual meeting, December
Number of members 17

PRESIDENT
Carroll, John J. .... Winsted
SECRETARY
Stifter, A. J. .... Winsted
‡ Blackwell, Leonard H. .... Hutchinson
‡ Bretzke, Carl O. .... Hutchinson
Carroll, John J. .... Winsted
‡ Griebie, Grant L. .... Hutchinson
‡ Hegrenes, Robert L. .... Hutchinson
‡ Huebert, Dan W. .... Hutchinson
‡ Jensen, Alvin M. .... Brownton
‡ Lippmann, Elmer W. .... Hutchinson
‡ McCoy, Donald E. .... Glencoe
‡ McNeil, Maurice R. .... Glencoe
‡ Navratil, Donald R. .... Glencoe
‡ Neumaier, Arthur .... Glencoe
‡ Peterson, Kenneth H. .... Hutchinson
‡ Selmo, Joseph D. .... Norwood
‡ Smith, George R. .... Hutchinson
‡ Smyth, John J. .... Lester Prairie
Stifter, A. J. .... Winsted
‡ Truesdale, Clark W. .... Saudi Arabia

MOWER COUNTY MEDICAL SOCIETY

Mower County
Regular meetings, last Friday of the month
Annual meeting, November
Number of members 35

PRESIDENT

	Pesonen, Clifford	Austin

SECRETARY

	Todd, John C.	Austin
‡	Anderson, David P., Jr.	Austin
‡	Anderson, Harold J.	Austin
‡	Barber, Tracy E.	Austin
‡	Christian, William L.	Austin
‡	Cronwell, Bernhard J.	Austin
	Elliott, Harold J.	Hayfield
‡	Hagen, John D.	Austin
†	Hertel, Garfield E.	McAllen, TX
‡	Hesla, Inman A.	Austin
‡	Isele, Reginald H.	Austin
†	Leck, Paul C.	Palm Desert, CA
‡	Lommen, M. L.	Austin
†‡	Lommen, Peter A.	Austin
	Lommen, Peter A., Jr.	Austin
†	McKenna, Jay K.	LaJolla, CA
‡	Miller, Herman	Austin
‡	Mlinar, Joseph P.	Austin
†	Morse, Morton P.	LeRoy
	Morse, Roger D.	LeRoy
‡	Muchow, Gene C.	Austin
‡	O'Rourke, William J.	Austin
‡	Patten, John C.	Austin
	Pesonen, Clifford A.	Austin
‡	Peterson, Stanley C.	Austin
‡	Roberts, George A.	Austin
†	Robertson, Paul A.	Austin
‡	Rosenthal, F. Harold	Austin
	Schneider, Paul J.	Adams
†	Smythe, Gwendolyn S.	Austin
‡	Smythe, Lowell J.	Austin
	Stahl, G. W.	Austin
‡	Taufic, Mansur	Austin
†	Thomson, James M.	Austin
‡	Todd, John C.	Austin
	Twiggs, Leo F.	Austin
	Van Cleve, H. P., Jr.	Austin

NICOLLET-LeSUEUR COUNTY MEDICAL SOCIETY

Nicollet and LeSueur Counties
Regular meetings, first Monday of even months
Annual meeting, December
Number of members 22

PRESIDENT

	Grimes, Burton P.	St. Peter

SECRETARY

	Olmanson, Vern	St. Peter

‡	Anderson, Jo E.	LeSueur
†	Branham, Donald S.	Hastings
	Brink, Donald	St. Peter
‡	Engstrom, George E.	St. Peter
‡	Grimes, Burton P.	St. Peter
‡	Haes, Julius E.	St. Peter
‡	Hiniker, Peter J.	St. Peter
	Koskela, L. E.	St. Peter
	Larson, Milo H.	St. Peter
‡	Lenander, Mellvin E. L.	St. Peter
‡	Olmanson, Edmund G.	St. Peter
	Olmanson, M. Donald	St. Peter
‡	Olmanson, Vern	St. Peter
†	Sauer, Jean C.	Ft. Snelling
	Schwartz, Carl	St. Peter
‡	Sheppard, Charles G.	St. Peter
‡	Sjostrom, Lawrence E.	St. Peter
‡	Sonnesyn, Nels N.	LeSueur
‡	Strathern, Carleton S.	St. Peter
	Thompson, A. Henry	St. Peter
‡	Walden, A. Don	LeSueur
‡	Wohlrabe, Clarence F.	North Mankato

PARK REGION DISTRICT AND COUNTY MEDICAL SOCIETY

Douglas, Grant, Otter Tail and Wilkin Counties
Regular meetings, March, June, September and December
Annual meeting, December
Number of members 59

PRESIDENT

	Shaver, Ward	Fergus Falls

SECRETARY

	Orandi, Ahmad	Fergus Falls
	Akhavan, Traz H.	Alexandria
†	Arndt, Harry W.	Detroit Lakes
	Baker, Jeannette L.	Fergus Falls
	Baker, Norman H.	Fergus Falls
‡	Bateman, Clarence V.	Fergus Falls
‡	Bhattacharyya, Sisir K.	Battle Lake
	Boline, Clifford A.	Battle Lake
‡	Cain, James H.	Alexandria
‡	Carlson, Carl E.	Alexandria
	Carlson, Homer J.	Pelican Rapids
	Clifford, George W.	Alexandria
	Colman, Edward L.	Fergus Falls
	Doms, Vernon A.	Elbow Lake
	Emerson, Edwin E.	Osakis
	Engebretson, Paul	Alexandria
‡	Estrem, Ralph L.	Fergus Falls
	Estrem, Robert D.	Fergus Falls
	Geiser, Peter M.	Alexandria

Park Region District and County Medical Society

(Continued)

‡	Hanson, Everett C.	New York Mills
‡	Heegaard, William G.	Alexandria
‡	Helseth, Hovald K.	Fergus Falls
‡	Hom, Leong Y. W.	Fergus Falls
†	Houkom, Bjarne	Fergus Falls
‡	Jacobson, Clifford W.	Breckenridge
	Jorgensen, Edward O.	Fergus Falls
‡	Kevern, Jay L.	Henning
‡	Kippen, Neil	Breckenridge
‡	Korda, Henry A.	Pelican Rapids
‡	Kuhlmann, Vernon G.	Alexandria
	Larson, Dorette W.	Fergus Falls
‡	Lewis, Charles W.	Henning
*†	Love, Frederick A.	Carlos
	Lu, Cheng-en	Fergus Falls
	Lueders, James	Evansville
‡	Lund, Carl J. T.	Fergus Falls
†	Mortensen, Nels G.	St. Paul
‡	Mouritsen, Glenn J.	Fergus Falls
‡	Nicholson, Richard W.	Fergus Falls
	O'Brien, Louis T.	Breckenridge
	Olson, Frances P.	Fergus Falls
‡	Orandi, Ahmad	Fergus Falls
	Orandi, Mehdi	Fergus Falls
†	Ostergaard, Erling	Elbow Lake
†	Patterson, William L.	Fergus Falls
	Perkins, Douglass E.	Alexandria
	Reinhardt, James H.	Alexandria
‡	Richter, Paul H.	Fergus Falls
‡	Rockwood, Philo H.	Fergus Falls
‡	Sanderson, David J.	Fergus Falls
	Schoeneberger, P. B.	Perham
‡	Sethre, Arthur E.	Fergus Falls
‡	Shaver, Ward	Fergus Falls
	Sporre, Knute A.	Fergus Falls
	Stemsrud, Harold L.	Alexandria
	Struthers, Lewis	Parkers Prairie
‡	Syverson, Leslie A.	Fergus Falls
†‡	Tanquist, Edwin J.	Alexandria
	Tanquist, Edwin J., Jr.	Alexandria
‡	Undem, Dale	Alexandria
	Warner, James J.	Perham
	Wasson, Loren F.	Alexandria

RAMSEY COUNTY MEDICAL SOCIETY

Ramsey County
Regular meetings, last Monday each month except
June, July and August
Annual meeting in January
Number of members 580

PRESIDENT
Craig, David M. .... St. Paul
SECRETARY
Ravits, Harold G. .... St. Paul
EXECUTIVE SECRETARY
Aldean, Mrs. Sue .... St. Paul

	Abrams, Alexander, Jr.	St. Paul
‡	Adair, Albert F., Jr.	St. Paul
	Adams, Harold R.	St. Paul
‡	Adcock, Leon L.	St. Paul
‡	Ahrens, Robert M.	St. Paul
	Aksoy, Mustafa M.	St. Paul
‡	Albrecht, Raymond	St. Paul
‡	Alden, John F.	St. Paul
‡	Alton, Donald G.	St. Paul
‡	Amerongen, Werner W.	St. Paul
‡	Anderson, David W.	St. Paul
	Anderson, James J.	St. Paul
	Anderson, Margaret C.	St. Paul
‡	Anderson, Richard W.	St. Paul
‡	Arny, Frederick P.	St. Paul
‡	Antolak, Stanley J., Jr.	St. Paul
‡	Arzt, Philip K.	St. Paul
	Ashmore, Herbert C.	St. Paul
‡	Auran, David B.	St. Paul
‡	Aurelius, J. Richards	St. Paul
‡	Ausman, Duane R.	St. Paul
‡	Austrian, Sol	St. Paul
‡	Babb, Frank S.	St. Paul
	Bach, Jerome M.	St. Paul
‡	Bah, Merle C.	St. Paul
	Baker, Chilton R., Jr.	St. Paul
‡	Balce, Regino V.	St. Paul
	Bauer, Eugene L.	St. Paul
‡	Beck, Charles J.	North St. Paul
	Beckman, Donovan L.	St. Paul
‡	Beek, Harvey O.	St. Paul
‡	Beer, John J.	St. Paul
‡	Bellomo, James	St. Paul
	Belsito, Alphonso A.	St. Paul
‡	Belz, Reinmar	St. Paul
‡	Benepe, James L.	St. Paul
	Benthack, Elaine M.	New Brighton
†‡	Bernier, M. J.	North St. Paul
†	Bernstein, William C.	St. Paul
‡	Bieter, Thomas G.	St. Paul
#	Birkebak, Roland C.	St. Paul
	Black, Earl J.	White Bear Lake
	Blackburn, Henry W., Jr.	St. Paul
‡	Blomberg, William R.	St. Paul
	Blumberg, Henry B.	St. Paul
†	Bock, Rolland A.	St. Paul
	Boies, Lawrence R., Jr.	St. Paul
‡	Bonello, Frank J.	St. Paul
†	Bouma, Lewis R.	St. Paul
†	Brainard, John B.	St. Paul
‡	Briggs, John F.	St. Paul
‡	Briggs, Thomas G.	White Bear Lake
	Broadie, Thomas E.	St. Paul
†‡	Brodie, Walter D.	St. Paul
‡	Broman, Harold R., Jr.	North St. Paul
	Brown, Charles T.	St. Paul
#‡	Brown, Christopher J.	Mineral Wells, TX
‡	Brown, Hector M.	St. Paul
	Brown, James E., Jr.	St. Paul
‡	Brown, James P.	St. Paul
‡	Brown, John M.	St. Paul
‡	Bulinski, Theodore J.	St. Paul
‡	Burklund, Edwin C.	St. Paul
‡	Burlingame, David A.	St. Paul
‡	Burmeister, Richard O.	St. Paul
‡	Burns, John M.	St. Paul

Continued on Next Page

Ramsey County Medical Society *(Continued)*

‡	Burton, J. Richard	St. Paul
‡	Bush, Robert P.	St. Paul
‡	Byrne, William J.	St. Paul
‡	Cain, Clark L.	St. Paul
‡	Carey, Lewis S.	St. Paul
	Carley, Richard B.	St. Paul
	Cedarleaf, Cherry B.	White Bear Lake
†‡	Chatterton, Carl C.	St. Paul
‡	Cich, John A.	West St. Paul
‡	Clark, W. Bruce	St. Paul
‡	Cochrane, Byron B.	St. Paul
	Coddon, Walter D.	St. Paul
†‡	Colby, Woodard L.	St. Paul
	Cole, Wallace H.	St. Paul
‡	Coleman, John B.	St. Paul
‡	Colton, Roger S.	St. Paul
‡	Comfort, Thomas H.	Minneapolis
‡	Connolly, Coleman J.	St. Paul
‡	Connolly, Joseph P.	West St. Paul
†	Connor, Charles E.	St. Paul
†‡	Cook, C. Kenneth	St. Paul
	Cooper, Charles C.	Moose Lake
†	Countryman, Roger S.	Saratoga, CA
‡	Craig, David M.	St. Paul
‡	Cram, Barclay M.	St. Paul
	Cramer, Glen G.	New Brighton
	Crowley, James H.	St. Paul
‡	Crudo, Vincent D.	St. Paul
‡	Crum, Arthur Z.	St. Paul
†	Crump, James W.	St. Paul
‡	Culligan, John A.	St. Paul
‡	Culver, Lucian G.	St. Paul
‡	Cumming, E. Dale	St. Paul
‡	Daly, Alfred E.	St. Paul
‡	Damberg, Sheldon W.	St. Paul
‡	Davis, Edward V.	St. Paul
	Davis, Eunice A.	St. Paul
‡	Dawson, James R.	St. Paul
‡	Decker, Charles H.	St. Paul
‡	Derauf, Donald E.	St. Paul
‡	Derechin, William	St. Paul
‡	Deters, Donald C.	St. Paul
	Dietrich, Donald E.	St. Paul
†‡	Dittrich, Raymond J.	St. Paul
‡	Dolmage, George H.	St. Paul
‡	Dooley, Robert T.	St. Paul
‡	Dunn, Robert C.	St. Paul
‡	Durkin, John L.	St. Paul
	Duthoy, Everett J.	St. Paul
‡	Duvall, Arndt J., III	Minneapolis
‡	Dyrdal, Paul J.	St. Paul
	Earl, George A.	St. Paul
‡	Earl, John R.	St. Paul
	Edwards, J. Willard	St. Paul
‡	Edwards, Jesse E.	St. Paul
	Edwards, Lloyd G.	St. Paul
	Edwards, Richard B.	St. Paul
	Edwards, Thomas J.	St. Paul
‡	Eelkema, Herman H.	St. Paul
	Eginton, Charles T.	Fargo, ND
‡	Eilers, Vincent E.	St. Paul
	Emerson, Edward C.	St. Paul
	Ellis, Ronald W.	St. Paul
‡	Emmons, Robert W.	St. Paul
	Endress, Edward K.	St. Paul
‡	England, Rodney W.	St. Paul
†	Engstrand, Oscar J.	Minneapolis
‡	Enroth, Oscar E.	St. Paul
	Erlanson, A. Cornell	St. Paul
	Erling, Carl B.	St. Paul
‡	Ersfeld, Murray P.	St. Paul
‡	Farkas, John V.	St. Paul
‡	Fee, John G.	St. Paul
‡	Felder, Davitt A.	St. Paul
‡	Felion, Arthur J.	St. Paul
‡	Ferguson, John N.	St. Paul
†‡	Fesler, Harold H.	West St. Paul
‡	Fink, Daniel L.	St. Paul
‡	Fischer, Robert F.	St. Paul
‡	Fisher, Dan W.	St. Paul
‡	Flannery, Hubert F.	St. Paul
	Flom, Reynold P.	St. Paul
‡	Flom, Robert S.	St. Paul
‡	Flynn, Louis L., Jr.	St. Paul
‡	Flynn, Robert A.	St. Paul
†‡	Fogarty, Charles W.	St. Paul
‡	Fogelberg, Emil J.	St. Paul
‡	Foreman, Richard T.	St. Paul
	Forsythe, James R.	St. Paul
‡	Fox, LeRoy J.	St. Paul
‡	Freeman, Charles D., Jr.	St. Paul
	Fritz, Wallace L.	St. Paul
‡	Froats, Charles W.	St. Paul
‡	Frye, Charles W.	St. Paul
‡	Fuller, Benjamin F.	White Bear Lake
	Funke, Joyce L.	St. Paul
‡	Gaertner, Frank M. J., Jr.	St. Paul
‡	Gaertner, John R.	St. Paul
‡	Galligan, John J.	St. Paul
‡	Gardner, Walter P.	St. Paul
	Garrow, Douglas M.	St. Paul
	Gaute, Svend T.	St. Paul
†‡	Gehlen, Joseph N.	St. Paul
‡	Geist, Robert W.	St. Paul
‡	Gendron, Joseph L.	St. Paul
	Gibbs, Edward C.	St. Paul
‡	Gilchrist, Milton R.	St. Paul
‡	Gillespie, Delmar R.	St. Paul
†‡	Gilman, Lloyd C.	St. Paul
‡	Gilsdorf, Donald A.	St. Paul
*‡	Gleason, Wallace A.	St. Paul
‡	Glenny, William R.	St. Paul
‡	Goldberg, Robert J.	St. Paul
‡	Goldsmith, Joseph W.	St. Paul
	Goodman, Ernest	St. Paul
‡	Goott, Bernard	St. Paul
‡	Govrik, Kalman	St. Paul
‡	Greene, Jerry G.	St. Paul
‡	Gretsch, Gerald A.	St. Paul
	Gridley, John W.	Minneapolis
#‡	Griffin, Patrick J.	Atlanta, GA
‡	Griffin, Thomas M.	St. Paul
	Gudio, Felix A., Jr.	St. Paul
‡	Gumnit, Robert J.	St. Paul
‡	Guthrie, J. Cameron	St. Paul
	Hakanson, Erick Y.	St. Paul
‡	Hall, Barnard	St. Paul
‡	Hammes, Ernest M., Jr.	St. Paul
‡	Hannon, Donald W.	St. Paul
	Hanton, Edward M.	St. Paul
	Harmon, Gaius E.	St. Paul
‡	Harris, John E.	Minneapolis
‡	Harris, Max E.	St. Paul
‡	Hartfiel, William F.	St. Paul
	Hartig, Marjorie	St. Paul

Ramsey County Medical Society *(Continued)*

‡	Hauser, Charles W.	St. Paul
†‡	Hauser, Victor P.	St. Paul
‡	Hawkinson, Harlan W.	St. Paul
‡	Hayes, Albert F.	St. Paul
†‡	Heck, William W.	St. Paul
‡	Hedenstrom, Charles W.	St. Paul
†	Hedenstrom, Frank G.	St. Paul
‡	Hedenstrom, Richard H.	St. Paul
	Hedlund, Charles J.	St. Paul
‡	Heilig, William R.	St. Paul
‡	Henderson, Terrance	White Bear Lake
†	Hengstler, William H.	St. Paul
‡	Henke, Wilbert J.	St. Paul
‡	Henry, James S.	St. Paul
	Herman, Samuel M.	St. Paul
‡	Herrick, Donald W.	St. Paul
†	Hetzler, John A.	White Bear Lake
‡	Hilgedick, William R.	St. Paul
‡	Hilger, Jerome A.	St. Paul
‡	Hilger, John	St. Paul
‡	Hilger, Laurence D.	St. Paul
‡	Hilker, Marcus D.	St. Paul
	Hill, Charlotte W.	St. Paul
‡	Hinckley, Robert G.	White Bear Lake
†	Hiniker, Louis P.	St. Paul
‡	Ho, Shu Kang	St. Paul
‡	Hodgson, Corrin H.	St. Paul
	Hodgson, Jane E.	St. Paul
‡	Hohmann, Albert	St. Paul
†	Holcomb, O. William	St. Paul
‡	Hollinshead, William H.	St. Paul
‡	Holt, John E.	St. Paul
	Hopkins, G. Wendell	Minneapolis
‡	Hottinger, George C.	St. Paul
	Houlton, William H.	St. Paul
‡	Howe, Newell W.	West St. Paul
‡	Hunter, Samuel W.	St. Paul
‡	Hurwitz, Milton M.	St. Paul
‡	Huseby, Thomas L.	St. Paul
‡	Husebye, Kjeld O.	St. Paul
‡	Jackson, William C.	St. Paul
‡	James, Ellery M.	St. Paul
‡	James, John W.	St. Paul
#‡	Janecek, James, Jr.	Columbus, GA
‡	Janssen, Martin E.	St. Paul
	Jarvis, Charles W.	St. Paul
‡	Jastram, Rupert M.	St. Paul
*‡	Johanson, Waldemar G.	St. Paul
	Johnson, Carl E.	St. Paul
	Johnson, Carolyn A.	St. Paul
‡	Johnson, Herbert W.	St. Paul
‡	Johnson, Richard J.	St. Paul
‡	Johnson, Thomas E.	St. Paul
	Jorgensen, Donald R.	St. Paul
	Joseph, Arnold H.	St. Paul
	Kantar, Everett H.	St. Paul
	Kaplan, David H.	Minneapolis
‡	Kantar, Yale C.	St. Paul
‡	Karon, Everett H.	St. Paul
‡	Karon, Irvine M.	St. Paul
‡	Kasper, Eugene M.	St. Paul
	Katz, Louis J.	Long Beach, CA
‡	Kelly, Albert C.	St. Paul
‡	Kelly, Edward H.	St. Paul
	Kelly, Helen M.	St. Paul
‡	Kelly, Joseph R.	St. Paul
‡	Kelsey, Chauncey M.	St. Paul
‡	Kenefick, Emmett V.	St. Paul
‡	Kenyon, Thomas J.	St. Paul
†	Kesting, Herman	St. Paul
	Kleinsasser, Warren L.	Farmington
‡	Knutson, Gerhard E.	St. Paul
	Knutson, Robert C.	St. Paul
	Kodres, Nina	St. Paul
‡	Kosiak, Michael	St. Paul
	Koza, Donald W.	St. Paul
	Kraatz, Robert W.	St. Paul
‡	Kramer, James D.	St. Paul
‡	Krezowski, Thomas K.	St. Paul
‡	Kugler, Alex A.	St. Paul
‡	Kuske, Albert W.	St. Paul
‡	Kusske, Bradley W.	St. Paul
‡	Kusske, Douglas R.	St. Paul
‡	Kvam, Lowell	St. Paul
	Lade, Roswith I.	St. Paul
‡	LaFave, James W.	St. Paul
‡	Lampert, Ronald M.	St. Paul
‡	Lane, Miles I.	White Bear Lake
‡	Lannin, Bernard G.	St. Paul
‡	Lannin, Donald R.	St. Paul
	Larkin, John E.	St. Paul
	Larson, Eva Jane Ostergren	St. Paul
‡	Larson, Jerrold V.	St. Paul
‡	Laszewski, Franz Von Zelberschwecht	St. Paul
‡	Lawler, Kevin M.	St. Paul
‡	Lees, Jack R.	St. Paul
	Lehman, Donald S.	St. Paul
‡	Leick, Richard M.	St. Paul
†	Leitch, Archibald	St. Paul
‡	Leonard, Stanley	St. Paul
*†	Lepak, John A.	St. Paul
‡	Lerdahl, Kenneth	St. Paul
‡	Lerner, Irving J.	St. Paul
‡	Lessard, Richard J.	St. Paul
	Leven, N. Logan	St. Paul
‡	Leverenz, Carleton W.	St. Paul
‡	Levitan, Leonard H.	St. Paul
	Levitt, George X.	St. Paul
	Lewis, Joyce S., Jr.	Minneapolis
†‡	Lick, C. Louis	St. Paul
‡	Lick, William J.	St. Paul
‡	Lien, Richard J.	St. Paul
†	Lightbourn, Edgar L.	Hastings
‡	Lilleberg, Norbert J.	St. Paul
‡	Lillie, Andrew R.	St. Paul
‡	Lindell, Robert E.	St. Paul
‡	Lindquist, Max F.	South St. Paul
	Lippman, Hyman S.	St. Paul
	Litkewitsch, Helene	St. Paul
‡	Loken, Selmer M.	St. Paul
	Lowe, Alexander D.	South St. Paul
†	Lowe, Thomas A.	South St. Paul
‡	Lufkin, Murray W.	St. Paul
‡	Lundholm, Arthur M.	Harris
‡	Lunzer, Richard G.	St. Paul
‡	Lynch, Francis W.	St. Paul
‡	Lynch, Richard P.	St. Paul
‡	McCain, Donovan L.	St. Paul
‡	McCafferty, Charles W.	St. Paul
‡	McCarthy, Charles J.	St. Paul
†	McClanahan, Thomas S.	White Bear Lake
	McClellan, Robert J.	St. Paul
	McCloud, C. Naumann	St. Paul
‡	McEllistrem, Edward J.	St. Paul

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Ramsey County Medical Society *(Continued)*

‡	McEllistrem, Gerald D.	St. Paul
‡	McEwan, Alexander	St. Paul
‡	McGroarty, Brian J.	St. Paul
‡	McHutchinson, Samuel K.	St. Paul
	McKenzie, Eva E.	St. Paul
‡	McNeill, John A.	St. Paul
‡	MacCornack, Robert L., Jr.	South St. Paul
	Mackoff, Sam M.	Phoenix, AZ
	Madland, Robert S.	St. Paul
#	Magary, Victor J., Jr.	So. Ft. Mitchell, KY
‡	Malerich, J. Anthony	West St. Paul
‡	Manlove, Charles H., Jr.	St. Paul
‡	Marta, John B.	St. Paul
‡	Martin, Dwight L.	St. Paul
†‡	Martineau, Joseph L.	St. Paul
	Maruyama, Yosh	St. Paul
	Mateo, Guillermo	St. Paul
	Matthews, James H.	Minneapolis
	Matus, Richard N.	St. Paul
‡	Mazzitello, William F.	St. Paul
‡	Mears, Burtis J.	St. Paul
‡	Medelman, John P.	St. Paul
‡	Melancon, Joseph F.	St. Paul
‡	Merrick, Robert L.	St. Paul
‡	Michienzi, Leonard J.	St. Paul
‡	Miller, Albert G.	St. Paul
‡	Miller, Winston R.	St. Paul
	Miller, Zondal R.	St. Paul
‡	Milnar, Frank J.	St. Paul
	Milroy, Thomas W.	Minneapolis
‡	Mishek, Charles J.	St. Paul
‡	Mitchell, George S.	St. Paul
†	Molander, Herbert A.	St. Paul
‡	Monahan, Robert H.	St. Paul
‡	Mooney, Robert D.	St. Paul
	Moren, J. Adelaide	St. Paul
‡	Mowlem, Albert	St. Paul
‡	Muller, A. Eugene	North St. Paul
	Mundahl, Harold R.	St. Paul
	Murphy, Jack T.	St. Paul
‡	Neher, Frederick J.	St. Paul
‡	Nelson, Delbert R.	St. Paul
‡	Nelson, Loren E.	St. Paul
‡	Nelson, Louis A.	St. Paul
‡	Nelson, Ronald J.	St. Paul
	Nesvacil, Leon	St. Paul
‡	Nichols, Thomas O.	St. Paul
‡	Nimlos, Kenneth O.	St. Paul
†	Nimlos, Lenore O.	St. Paul
	Norman, David D.	St. Paul
	Norquist, Joseph L.	St. Paul
	Nuebel, Charles J.	Long Beach, CA
†	Nye, Lillian L.	St. Paul
	O'Brien, Gerald R.	Minneapolis
‡	O'Brien, John C.	St. Paul
‡	O'Kane, Thomas W.	St. Paul
‡	O'Malley, Valentine	St. Paul
	O'Neill, Nial C.	St. Paul
†	O'Reilley, Bernard E.	Sun City, AZ
	Ockuly, Orville E.	St. Paul
†	Ogden, Warner	St. Paul
†	Ohage, Justus	St. Paul
‡	Olsen, Ralph L.	St. Paul
	Olson, Barbara F.	Minneapolis
‡	Osekowsky, Henry J.	St. Paul
†‡	Ostergren, Edward W.	St. Paul
‡	Ouellette, Alfred	St. Paul
‡	Owens, Frederick M., Jr.	St. Paul
‡	Palm, Neil M.	St. Paul
‡	Paulson, Elmer C.	St. Paul
‡	Paulson, Wallace J.	St. Paul
†	Pearson, Fritz R.	St. Paul
‡	Pearson, Malcolm M.	St. Paul
†	Pedersen, Arthur H.	St. Paul
‡	Perry John F., Jr.	St. Paul
‡	Peterson, Donald H.	St. Paul
‡	Peterson, Edward A.	St. Paul
‡	Peterson, Harold O.	Minneapolis
†	Peterson, Joel L. E.	St. Paul
	Peterson, Roy L.	White Bear Lake
	Phillips, Leonard	St. Paul
‡	Pilney, Frank T.	St. Paul
‡	Plotke, Harry L.	St. Paul
	Polski, Paul G.	South St. Paul
‡	Post, Edmund A.	St. Paul
‡	Powers, Robert L.	St. Paul
†	Prentice, Walter B.	St. Paul
‡	Proud, Harry S.	St. Paul
	Quattlebaum, Frank W.	St. Paul
‡	Raaen, Olaf J.	St. Paul
	Rabcevich, Anatole	St. Paul
‡	Ralph, James R.	St. Paul
‡	Ramlow, Ralph M.	West St. Paul
†	Ramsey, Walter R.	St. Paul
	Rasmussen, Ramby C.	St. Paul
‡	Raths, Otto N., Jr.	St. Paul
‡	Ravits, Harold G.	St. Paul
‡	Rea, Charles E,	St. Paul
	Redleaf, Paul D.	St. Paul
‡	Reid, James W.	South St. Paul
‡	Reif, Robert W.	White Bear Lake
‡	Richardson, Edward J., Jr.	St. Paul
‡	Rick, Paul F. W.	St. Paul
‡	Rinkey, Eugene	St. Paul
†	Ripple, Rudolph J.	St. Paul
*‡	Ritchie, Wallace P.	St. Paul
†‡	Ritt, Albert E.	St. Paul
‡	Roach, Charles A.	St. Paul
‡	Roach, Donald E.	St. Paul
‡	Rolig, David H.	West St. Paul
	Rollie, Orris O.	St. Paul
†‡	Rosenthal, Robert	St. Paul
	Rossing, Robert G.	Brooks AFB, TX
‡	Roth, George C.	St. Paul
‡	Rowe, Clarence J., Jr.	St. Paul
‡	Roy, Philemon C.	St. Paul
†	Ruhberg, George N.	Santa Barbara, CA
‡	Rukavina, John G.	St. Paul
‡	Rushay, Arthur J.	White Bear Lake
‡	Rusterholz, Alan P.	St. Paul
†‡	Ryan, John J.	St. Paul
‡	Ryan, Joseph M.	St. Paul
‡	Sand, Richard E.	St. Paul
‡	Sandkamp, Virgil A.	South St. Paul
‡	Sargent, John H.	St. Paul
‡	Schaffhausen, George E.	St. Paul
‡	Scherek, Jerome J.	St. Paul
‡	Schloff, Ivan	St. Paul
‡	Schloff, Leonard D.	St. Paul
	Schmidtke, Reinhardt L.	Minneapolis
†	Schoch, Robert B. J.	St. Paul
‡	Schochet, H. Laurence	St. Paul
†	Schons, Edward	Minnetonka Beach
‡	Schossow, George W.	White Bear Lake
‡	Schrader, Wayne H.	St. Paul

Ramsey County Medical Society *(Continued)*

‡	Schroeckenstein, Hugo F.	St. Paul
*	Schwyzer, Marguerite	St. Paul
‡	Scott, Eugene E.	St. Paul
	Sekhon, Mohan S.	St. Paul
‡	Sells, Richard J.	St. Paul
†‡	Setzer, Hobert J.	St. Paul
†	Shannon, William R.	Faribault
	Shear, Howard H.	West St. Paul
‡	Shelander, Marcus I.	St. Paul
	Short, Marshall H.	St. Paul
	Simmonds, Harry N. L.	St. Paul
‡	Simons, Leander T.	St. Paul
	Siegel, Clarence	St. Paul
‡	Singer, Benjamin J.	St. Paul
‡	Skinner, Abbott	St. Paul
†	Skinner, Harvey O.	St. Paul
‡	Smiley, Donald P.	St. Paul
‡	Smisek, Elmer A.	St. Paul
‡	Smith, H. Nippert	St. Paul
‡	Smith, Vernon D. E.	St. Paul
‡	Smith, William T.	St. Paul
†	Snyder, George W.	St. Paul
†‡	Sohlberg, Olof I.	St. Paul
‡	Sommerdorf, Vernon L.	St. Paul
‡	Sorem, Milton B.	St. Paul
‡	Soucheray, Philip H.	St. Paul
†‡	Souster, Benjamin B.	St. Paul
‡	Sowada, Ernest J.	St. Paul
‡	Sperl, Michael P., Jr.	St. Paul
‡	Sprafka, Gregory A.	St. Paul
‡	Sprafka, Joseph L.	St. Paul
‡	Spraitz, Anton F., Jr.	St. Paul
‡	Stafne, John G.	St. Paul
‡	Stein, Robert L.	North St. Paul
‡	Steinberg, Charles L.	St. Paul
	Stengl, Thomas A.	St. Paul
‡	Sterner, Donald C.	St. Paul
‡	Sterner, Ernest R.	St. Paul
‡	Sterner, John J.	St. Paul
‡	Stolee, Thomas A.	St. Paul
	Straus, Maurice L.	St. Paul
‡	Strem, Edward L.	St. Paul
‡	Sturley, Rodney F.	St. Paul
‡	Sullivan, W. Albert, Jr.	St. Paul
‡	Swanson, Lawrence J.	West St. Paul
‡	Swanson, Ralph H.	West St. Paul
†	Swendson, James J.	St. Paul
‡	Swenson, Donald B.	St. Paul
‡	Taddeini, Luigi	St. Paul
‡	Tanasichuk, Murray A.	St. Paul
‡	Tani, George	St. Paul
	Tate, Wayne E.	South St. Paul
‡	Teeter, Richard R.	St. Paul
‡	Teisberg, John E.	St. Paul
‡	Thompson, Wayne W.	St. Paul
‡	Tiffany, Francis B.	St. Paul
‡	Tifft, Cyril R.	St. Paul
‡	Tongen, Lyle A.	St. Paul
‡	Travis, James S.	St. Paul
	Tregilgas, Richard B.	St. Paul
‡	Trotman, Neil M.	St. Paul
	Tveten, Omar A.	St. Paul
‡	Ubel, Frank A.	St. Paul
	Vail, David J.	St. Paul
	Van Bergen, Frederick H.	Minneapolis
‡	Van DeRiet, Lowell W.	St. Paul
‡	Varco, Richard L.	St. Paul
‡	Vaughn, C. Gordon	St. Paul
	Veinbergs, Arnold	St. Paul
	Veirs, Dean M.	Hastings
†	Veirs, Ruby J. S.	Hastings
†	Venables, Alexander E.	Marysville, WA
‡	Venters, Homer D., Jr.	St. Paul
‡	Votel, Thomas W.	St. Paul
†	Waas, Charles W.	St. Paul
‡	Walker, Arthur E.	St. Paul
‡	Wall, James O.	St. Paul
‡	Walsh, Edward F.	St. Paul
‡	Walter, Clarence W.	St. Paul
‡	Warner, Clyde M.	St. Paul
‡	Warren, Cecil A.	St. Paul
‡	Waters, Alvin W.	St. Paul
‡	Watson, P. Theodore	St. Paul
‡	Watson, William H. A.	St. Paul
‡	Watson, William J.	Newport
	Watz, Clarence E.	St. Paul
‡	Webber, Fred L.	St. Paul
‡	Wedes, Deno J.	St. Paul
#	Wegleitner, Mark J.	Fort Sill, OK
‡	Weigant, Charles E.	Fort Snelling
‡	Weis, Benjamin A.	St. Paul
‡	Weisberg, Maurice	St. Paul
‡	Wenzel, Gilbert P.	St. Paul
†	Westermeyer, Joseph J.	St. Paul
‡	Westover, Darrell E.	St. Paul
	Wetteland, Thomas F.	West St. Paul
‡	Wetzel, Earl V.	St. Paul
	Whiting, F. Douglas	St. Paul
	Wiencke, William M.	St. Paul
‡	Wier, G. Thomas	St. Paul
†‡	Williams, Clayton K.	St. Paul
‡	Williams, George E.	St. Paul
‡	Williams, Hugh J.	St. Paul
‡	Williams, John A.	St. Paul
	Williams, Richard A.	St. Paul Park
	Wilson, Fred B.	St. Paul
‡	Winter, Robert B.	St. Paul
	Wolfson, Justin J.	St. Paul
	Wolkoff, Hyman J.	St. Paul
‡	Woodburn, Robert L.	St. Paul
‡	Woolfrey, Bertram F.	St. Paul
	YaDeau, Richard E.	St. Paul
	Youngren, Everett R.	St. Paul
‡	Zachman, Leo L.	St. Paul
‡	Zagaria, James F.	St. Paul
‡	Zarling, Max E.	St. Paul

RANGE MEDICAL SOCIETY

Koochiching, Itasca and the Northern Portion of
St. Louis County
Regular meetings, fourth Tuesday of the Month
Annual meeting, January.
Number of members 109

PRESIDENT

	Erickson, Vernon D.	Grand Rapids

SECRETARY

	Balderson, Robert P.	Grand Rapids

CORRESPONDING SECRETARY

	Workman, Mrs. Rae	Hibbing

	Addy, Edward R.	Gilbert
‡	Ahola, Kenneth E.	Hibbing
	Alexander, Paul J.	Hibbing
	Anderson, Russell H.	Virginia
	Antonelli, Jordan J.	Hibbing
	Antonow, Arthur M.	Virginia
	Baich, Velemir M.	Coleraine
	Balderson, Robert P.	Grand Rapids
	Baraga, Anthony R.	Hibbing
‡	Barnes, Richard E.	Aurora
	Bartholdt, H. Peter	Cook
†	Benell, Otto E.	Britt
*†	Binet, Henry E.	Grand Rapids
#	Birkemeyer, Eugene J.	Mountain Home AFB, ID
	Bolz, J. Arnold	Grand Rapids
	Bonner, John L.	Grand Rapids
	Braun, Ohrmundt C.	Grand Rapids
	Brende, Joel O.	Littlefork
	Brockway, Roger W.	Grand Rapids
†	Cantwell, William F.	International Falls
	Chermak, Francis G.	Phoenix, AZ
‡	Ciriacy, Edward W.	Ely
	Cope, Hershel B.	Virginia
	Coy, Douglas J.	Grand Rapids
‡	Crow, George M.	International Falls
	DeMarais, Lloyd C.	Hibbing
	Dobler, Manfred G.	Ely
‡	Eisenman, Walter	Hibbing
	Engelstad, Wendell P.	Eveleth
‡	Erickson, Vernon D.	Grand Rapids
	Evensta, John B.	Grand Rapids
	Ewens, George B.	Virginia
‡	Ferrell, Clarence R.	Grand Rapids
‡	Flynn, Bernard F.	Hibbing
‡	French, Bayard T.	Hibbing
	Friedlieb, Oskar P.	Virginia
	Gerend, Thomas J.	Virginia
	Glomstad, Gary B.	Deer River
‡	Grahek, Jack P.	Ely
	Grinley, Andrew V.	Grand Rapids
‡	Halper, Bernard	Hibbing
	Halverson, Kermit J.	Parkville
‡	Hanover, Ralph D.	International Falls
	Hansen, Robert E.	Hibbing
	Hanson, Bernard H. P.	Bigfork
‡	Heiam, William C.	Cook
‡	Helwig, Karl L.	Virginia
	Ibrahim, George W.	Virginia
†	Ireland, Gerald W.	St. Paul
	Jacobson, Clarence	Chisholm
‡	Johnson, Calvin J.	Grand Rapids
‡	Johnsrud, Luverne	Hibbing
	Johnston, H. Wayne	Virginia
	Karges, Laurel E.	Grand Rapids
	Karish, Louis J.	Grand Rapids
	Kelly, Robert T.	Grand Rapids
	Kiesler, Frank	Grand Rapids
‡	Kotchevar, Frank R.	Minneapolis
	Law, Harrison E.	Virginia
	Leach, Thomas C.	Babbitt
‡	Lee, William C.	Hibbing
	McClelland, John G.	Virginia
	McKenna, John J.	Virginia
‡	McKenna, Maurice J.	Grand Rapids
	McQuoid, David W.	Littlefork
	Martinson, Raymond M.	Virginia
‡	Mast, Fredric L.	Chisholm
‡	Miettunen, John B.	Hibbing
	Miks, George M.	Aurora
	Mock, Charles J.	Virginia
‡	Moyer, Richard R.	Hibbing
	Mueller, Donald R.	Grand Rapids
‡	Muller, John J.	Hibbing
‡	Murray, Robert A.	Hibbing
‡	Neff, Walter S.	Britt
	Nelimark, Donald R.	Virginia
	Nixon, Rodney T. H.	Grand Rapids
‡	Nollet, Donald J.	Hibbing
	Owens, Ben P.	Hibbing
‡	Paciotti, Vincent J.	Hibbing
‡	Parker, Wilbert H.	Chisholm
	Payne, Richard E.	Virginia
	Perpich, Irene Kosiak	Virginia
	Person, Duane F.	Virginia
	Peterson, Edward N.	Virginia
	Prlina, Isaac M.	Virginia
	Reed, Paul	Virginia
	Reynolds, Dermot F.	Hibbing
	Richter, David J.	Virginia
	Roth, Albert H.	Deer River
†	Rowles, Everett K.	Laguna Hills, CA
‡	Salter, Reginald A.	Virginia
‡	Schirber, Martin J.	Grand Rapids
‡	Schweiger, Theodore R.	Hibbing
	Sher, David A.	Virginia
	Siegel, John S.	Virginia
†‡	Sinamark, Andrew	Hibbing
†	Sisler, Clifford E.	Grand Rapids
	Snyker, Omer E.	Ely
	Stolen, Keith H.	Grand Rapids
	Summar, M. Thomas	Virginia
	Swenson, Floyd J.	Grand Rapids
	Tietz, Charles A.	Virginia
‡	Walker, Stuart B.	Aurora
‡	Walter, Frederick H.	International Falls
	Weir, Mathew J.	Virginia
‡	Werner, Donald L.	Hoyt Lakes
	Wheeler, Gilbert S.	Virginia
	Wong, Howard H.	Virginia
‡	Woodruff, Whitney	Virginia

RED RIVER VALLEY MEDICAL SOCIETY

Kittson, Mahnomen, Marshall, Norman, Pennington, Polk,
Red Lake and Roseau Counties
Regular meetings, quarterly
Annual meeting, December
Number of members 51

PRESIDENT
Sather, Russell O. .... Crookston
SECRETARY
Clapp, Hubert D. .... Crookston
Baab, Robert O. .... Crookston
‡ Behr, Orlo K. .... Crookston
‡ Berg, Arnold M. .... Thief River Falls
† Bratrud, Edward .... Alexandria
Bray, Jerome L. .... Thief River Falls
‡ Brown, Glenn W. .... Halstad
Cameron, John H. .... Clovis, NM
‡ Clapp, Hubert D. .... Crookston
Dagg, Earl .... Thief River Falls
Davidson, Duane J. .... Thief River Falls
‡ Delmore, John L. .... Roseau
Dillenburg, Cyril .... Crookston
†‡ Flancher, Leon H. .... Detroit Lakes
†‡ Foderick, Peter P. .... Circle Pines
‡ Herber, Leo .... Thief River Falls
‡ Hirsh, Stanton .... Crookston
Holm, Owen W. .... Crookston
‡ Holmstrom, Carle H. .... Warren
Hunt, Vincent R. .... Red Lake Falls
‡ Klefstad, Lloyd H. .... Greenbush
†‡ Kostick, William R. .... Fertile
Leonardson, Peter Y. .... Red Lake Falls
‡ Loken, Theodore .... Ada
† Lynde, Orrin G. .... Los Gatos, CA
‡ Martin, George B. .... Thief River Falls
Mercil, Charles B. .... Mahnomen
‡ Mercil, William F. .... Crookston
† Montaniel, Necito L. .... Crookston
† Nelson, Henry E. .... Crookston
†‡ Oppegaard, C. L. .... Scottsdale, AZ
Pinsonneault, W. A. .... Roseau
#‡Pollman, Stanley E. .... Naha, Okinawa
‡ Pumala, Erven E. .... Warren
‡ Reff, Alan R. .... Crookston
† Roholt, Christian L. .... McIntosh
Rubin, Jacob S. .... Crookston
Russ, Homer H. .... Warroad
† Sather, R. Alan .... Dallas, TX
Sather, Edgar L. .... Fosston
‡ Sather, George A. .... Fosston
‡ Sather, Richard N. .... Fosston
‡ Sather, Russell O. .... Crookston
Scheuneman, Allen F. .... Thief River Falls
Schnabel, Norma B. .... Crookston
Schnabel, Robert F. .... Crookston
†‡ Skogerboe, Rudolph B. .... Minneapolis
‡ Stadem, Clifford .... Crookston
‡ Stewart, Donald E. .... Crookston
‡ Thorsgard, Ernest O. .... Thief River Falls
‡ Uhley, Charles G. .... Palm Desert, CA
Wendt, Paul .... Thief River Falls
‡ Wikoff, Howard M. .... Crookston

RENVILLE-REDWOOD COUNTY MEDICAL SOCIETY

Renville and Redwood Counties
Regular meetings, March, June, September and December
Annual meeting, December
Number of members 14

PRESIDENT
Ceplecha, Stanley F. .... Redwood Falls
SECRETARY
Flinn, James B. .... Redwood Falls
‡ Anderson, Chester A. .... Hector
Bingham, George C. .... Olivia
† Brand, William A. .... Redwood Falls
‡ Ceplecha, Stanley F. .... Redwood Falls
Cosgriff, James A., Jr. .... Olivia
† Diessner, A. W. .... Redwood Falls
‡ Eilers, William B. .... Redwood Falls
†‡ Fawcett, Arthur M. .... Renville
‡ Flinn, James B. .... Redwood Falls
‡ Furr, Leo O. .... Bird Island
‡ Gilles, Thomas .... Fairfax
‡ Lenz, Joseph R. .... Morton
‡ Nelson, Glenn E. .... Redwood Falls
‡ Strauchler, John .... Belview

RICE COUNTY MEDICAL SOCIETY

Rice County
Regular meetings, third Tuesday of
January, April, September and November
Annual meeting in November
Number of members 26

PRESIDENT
Speckhals, Robert C. .... Faribault

SECRETARY
Tuma, Ben .... Faribault

‡ Beaton, J. Gordon .... Northfield
‡ Bruhl, Heinz H. .... Faribault
Buesgens, Ralph H. .... Waterville
† Clarke, Dean .... Faribault
‡ Engberg, Edward J. .... Faribault
† Francis, David W. .... Morristown
Good, Roy H. .... Northfield
‡ Graham, Asa B. .... Faribault
‡ Haas, Jack F. .... Northfield
‡ Halvorson, David C. .... Northfield
† Kennedy, George L. .... Faribault
Kolars, James J. .... Faribault
*† Lende, Norman .... Faribault
Meyer, Paul F. .... Faribault
Meyer, Richard H. .... Faribault
Meyer, Robert P. .... Faribault
‡ Neutzman, Arthur W. .... Faribault
‡ Orr, Burton A. .... Faribault
Rumpf, Carl W. .... Faribault
‡ Searl, Richard H. .... Faribault
‡ Smith, Thorsten .... Thiells, NY
‡ Street, Bernard .... Northfield
Studer, Donald J. .... Faribault
† Traeger, Carl A. .... Faribault
Tuma, Ben .... Faribault
Watts, George W. .... Willard, NY
‡ Weaver, Paul H. .... Faribault

ST. LOUIS COUNTY MEDICAL SOCIETY

Carlton, Cook, Lake and Southern portion of
St. Louis County
Regular meetings, second Thursday in each month
except July and August
Annual meeting, second Thursday in January
Number of members 201

	PRESIDENT	
	Fisketti, Henry	Duluth
	SECRETARY	
	Meyer, Howard J.	Duluth
	SECRETARY, EXECUTIVE OFFICE	
	Lundgren, Miss Margaret M.	Duluth
‡	Abraham, Arden L.	Duluth
‡	Ahrens, Curtis F.	Duluth
‡	Anderson, James M.	Duluth
‡	Asta, Joseph J.	Duluth
†	Athens, A. G.	Santa Barbara, CA
‡	Atmore, William G.	Duluth
‡	Aufderheide, Arthur C.	Duluth
‡	Backus, Byron C.	Cloquet
‡	Backus, Lloyd B.	Cloquet
	Backus, Reno W.	Nopeming
‡	Bagley, Charles M.	Duluth
	Bagley, Elizabeth C.	Duluth
‡	Bakkila, Henry E.	Duluth
‡	Balmer, Albert I.	Duluth
*‡	Bardon, Richard	Duluth
‡	Barker, John D.	Duluth
†	Barney, Leon A.	Duluth
‡	Barrett, Earl E.	Duluth
‡	Bartzen, Peter J.	Duluth
‡	Becker, Frederic T.	Duluth
‡	Bell, Harry M., Jr.	Duluth
	Bepko, Marie K. (Mrs. Puumala)	Cloquet
*†	Berdez, George L.	Duluth
‡	Bergan, Robert O.	Duluth
†‡	Bianco, Anthony J.	Duluth
‡	Bloom, Joseph	Silver Bay
‡	Boecker, Bernhard	Duluth
	Boman, Paul G.	Duluth
‡	Boyer, Samuel H.	Duluth
‡	Bray, Philip N	Duluth
‡	Brooker, Warren J	Duluth
‡	Brown, Cyrus C., Jr.	Duluth
‡	Buckley, Robert P.	Duluth
‡	Bulluck, Matthew H.	Duluth
‡	Butler, John K.	Cloquet
‡	Campaigne, Robert J.	Duluth
‡	Christensen, Clarence H.	Duluth
	Church, Gerald E.	Two Harbors
	Clark, Elizabeth A. (Mrs. Halbert)	Duluth
‡	Clark, Ivan T.	Duluth
‡	Coll, James J.	Duluth
†	Collins, Arthur N.	Duluth
‡	Conley, Francis W.	Duluth
‡	Cottor, Robert E.	Duluth
‡	Coventry, William D.	Duluth
	Cowan, Gary A.	Duluth
‡	Cowan, George M.	Duluth
‡	Creps, James R.	Duluth
	Davis, William	Moose Lake
‡	Deutsch, Robert J.	Duluth
‡	Dickson, Franklin H.	Proctor
‡	Dobbs, Richard L.	Duluth
‡	Drexler, Charles J.	Duluth
‡	Dwyer, John J.	Duluth
‡	Eckman, Philip F.	Duluth
‡	Eckman, Philip L.	Duluth
‡	Eckman, Ralph J.	Duluth
‡	Eklund, Carl D.	Duluth
‡	Emanuel, Karl W.	Duluth
	Engelsgjerd, Gerald L.	Duluth
	Evison, Emerson O.	Duluth
‡	Fawcett, Keith R.	Duluth
‡	Fellows, Manley F.	Duluth
‡	Feuling, John C.	Duluth
‡	Fifield, Malcolm M.	Duluth
‡	Fisketti, Henry	Duluth
‡	Fuller, Josiah	Duluth
‡	Gillespie, Malcolm G.	Duluth
†	Gobel, Fredarick L.	Minneapolis
‡	Goldish, Daniel R.	Duluth
‡	Goldish, Robert J.	Duluth
‡	Goldschmidt, Volker	Duluth
‡	Goodnow, William H.	Duluth
‡	Gowan, Lawrence R.	Duluth
‡	Gowan, Lawrence R., Jr.	Duluth
‡	Grohs, William H.	Duluth
‡	Gronquist, Y. K. J.	Cloquet
‡	Haase, Donald D.	Silver Bay
‡	Haavik, John E.	Duluth
	Halbert, John J.	Duluth
‡	Halliday, Phillip V.	Duluth
	Hanson, Ernest O.	Cloquet
‡	Harrington, Vernon A.	Duluth
‡	Heisel, John G.	Duluth
	Henry, Harold W.	Moose Lake
‡	Hilding, Anderson C.	Duluth
†	Hirschboeck, Frank J.	Duluth
‡	Hoeg, Dwight C.	Duluth
‡	Hoff, Herbert O.	Duluth
‡	Holt, Glen E.	Duluth
	Hood, Roderick P.	Duluth
‡	Houglum, Arvid J.	Duluth
‡	Houkom, S. Sverre	Duluth
	Hutchinson, Henry	St. Cloud
	Jacklin, Alexander J.	Duluth
‡	Jacobson, Ferdinand C.	Duluth
‡	Jacott, William E.	Duluth
†	Jensen, Thorvold J.	Duluth
‡	Jeronimus, Henry J.	Duluth
	Jessico, Charles M.	Duluth
‡	Johnson, Franklin L.	Duluth
‡	Johnson, Karl E.	Duluth
‡	Johnson, Theodore L.	Duluth
‡	Juntunen, Roy R.	Duluth
	Kilen, Mark	Duluth
†‡	Klein, Harry	Duluth
‡	Knoedler, John P.	Duluth
	Kosiak, William	Two Harbors
‡	Krueger, Victor R.	Nopeming
‡	Kundel, Donald W.	Duluth
	Kwako, Jerome E.	Duluth
‡	L'Abbe, A. J. Philip	Duluth
‡	LaBree, Robert H.	Duluth
#‡	Langseth, Rodney N.	Ft. Leavenworth, KS
‡	Larson, Donald M.	Duluth
	Larson, Keith I	Medical Lake, WA

St. Louis County Medical Society (Continued)

Larson, Kenneth R. ....Moose Lake
‡ Latterell, Kenneth E. ....Duluth
‡ Leek, Joseph H. ....Duluth
*† Lepak, Francis J. ....Duluth
Leppink, Harold B. ....Two Harbors
Leppo, N. Erkki A. ....Duluth
# Linke, Charles A. ....Fairport, NY
# Linke, Clara L. ....Fairport, NY
†‡ Litman, Samuel N. ....Duluth
†‡ McNutt, John R. ....Duluth
MacDonald, Roger A. ....Grand Marais
‡ MacRae, Gordon C. ....Duluth
† Magney, Fredolph H ....Duluth
Martin, Webster C. ....Duluth
‡ Maryland, Daniel L. ....Duluth
*† Mayne, Roy M. ....St. Paul
‡ Mendesh, Anthony N. ....Duluth
‡ Merrick, William G. ....Duluth
‡ Meyer, Howard J. ....Duluth
Michaelis, Dorothy ....Duluth
*† Moe, Thomas ....Moose Lake
Moller, Julie C. ....Duluth
Monge', James J. ....Duluth
‡ Monserud, Nels O. ....Cloquet
‡ Moyer, John B. ....Duluth
‡ Munger, James E. ....Duluth
Munson, Martin S. ....Moose Lake
‡ Nisius, George F. ....Duluth
‡ Nisswandt, Albert L. ....Duluth
†‡ Nordberg, Carl E. ....Los Altos, CA
‡ O'Neill, John C. ....Duluth
‡ Parson, E. Irvine ....Duluth
‡ Pasek, Antone W. ....Cloquet
Patch, Orien B. ....Duluth
‡ Pedersen, Roy C. ....Duluth
‡ Peterson, John H. ....Duluth
Pollard, William S. ....Duluth
‡ Power, John E. ....Duluth
Puumala, Barbara M. ....Cloquet
Puumala, Reino H. ....Cloquet
Puumala, Ricard R. ....Cloquet
‡ Reardon, Andrew E. ....Duluth
‡ Reed, Henry H. ....Duluth
Rowe, Richard G. ....Duluth
‡ Rudie, Peter S. ....Duluth
‡ Rudie, William D ....Duluth
‡ Runquist, John M. ....Duluth
‡ Ruth, Bradley R. ....Duluth
‡ Ryan, Edward A. ....Duluth
Sach-Rowitz, Alvan ....Moose Lake
Saloum, Lucille M. ....Duluth
Sanford, John B. ....Duluth
Sax, Milton H. ....Duluth
Sax, Simon G. ....Duluth
‡ Schmid, John F. ....Duluth
‡ Schneider, Lawrence E. ....Duluth
‡ Shirley, Raymond M. ....Duluth
Slack, William J. ....Duluth
‡ Smith, Cyril M. ....Duluth
Smith, Wallace R. ....Grand Marais
Spang, Anthony J. ....Duluth
‡ Spang, James S. ....Duluth
‡ Spang, William M. ....Duluth
‡ Stein, William A. ....Duluth
‡ Storsteen, Kenneth A. ....Duluth
‡ Streitz, John M. ....Duluth
‡ Strewler, Gordon J. ....Duluth
‡ Swedberg, William A. ....Duluth
‡ Swensen, Don P. ....Duluth
‡ Swenson, Arnold O. ....Duluth
Swenson, Orville P. ....Cloquet
Teich, Kenneth W. ....Pontiac, MI
‡ Terrell, Bernard J. ....Nopeming
‡ Tetlie, James P. ....Duluth
‡ Thomas, John V. ....Duluth
‡ Thompson, James I. ....Duluth
‡ Thurn, Roy J. ....Duluth
‡ Tosseland, Noel E. ....Duluth
‡ Ulrich, Emery E. ....Duluth
‡ Van Druten, William A. ....Duluth
‡ Van Puffelen, Paul S. ....Duluth
Van Ryzin, Donald J. ....Duluth
‡ Wahman, Robert E. ....Duluth
‡ Walder, Harold J. ....Duluth
‡ Wall, Jack E. ....Duluth
‡ Wallace, Martin O. ....Duluth
‡ Wells, Arthur H. ....Duluth
‡ Williams, Bruce F. P. ....Duluth
‡ Wolfe, John W. ....Duluth
‡ Young, Hadley R. ....Duluth

SCOTT-CARVER COUNTY MEDICAL SOCIETY

Scott and Carver Counties
Regular meetings, first Tuesday of each month,
except July and August
Annual meeting in June
Number of members 38

PRESIDENT
Pistulka, R. D. ....Chaska
SECRETARY
Wempner, Jon D. ....Waconia
‡ Adams, Patrick J. ....Shakopee
Amra, Waleed ....Chaska
Bean, Charles N. ....Waconia
‡ Bratholdt, James W. ....Watertown
† Buck, Frederick H. ....Shakopee
‡ Cervenka, Charles F. ....New Prague
Clarke, John W. ....Waconia
‡ Doherty, Elmer M. ....New Prague
‡ Erickson, Robert L. ....Rosemount
‡ Gildersleeve, Robert G. ....Watertown
‡ Hallgren, Roger B. ....Belle Plaine
† Hebeinsen, Milton B. ....Chaska
Heinz, Ivy ....Shakopee
‡ Heinzerling, Carl R. ....Chaska
†‡ Juergens, Herman M. ....Belle Plaine
† Kucera, Stanley T. ....Northfield
‡ Kuz, Eugene ....Savage
Larson, Leighton W. ....Waconia
‡ Lehrer, Alfred J., Jr. ....Montgomery
‡ Lukk, Olaf ....Prior Lake
† McDaniel, Samuel P. ....Lakeville
‡ Mendiola, Ramon P., Jr. ....Waconia
Moller, Jurgen ....Burnsville
‡ Nelson, Gerald E. ....Chaska
‡ Olson, Richard F. ....Chaska
‡ Pearson, Bror F. ....Shakopee

Continued on Next Page

Scott-Carver County Medical Society (Continued)

‡ Philp, David R. .... Watertown
‡ Pistulka, Rolland D. .... Chaska
‡ Ponterio, James E. .... Shakopee
Provence, Cecil L. .... Waconia
Rieschl, Elizabeth K. .... Jordan
Rynda, Edwin .... New Prague
Savaryn, John P. .... Waconia
‡ Schimelpfenig, George T. .... Chaska
† Smith, David G. .... Watertown
‡ Spagnolo, Anthony A. .... Shakopee
‡ Wempner, Jon D. .... Waconia
†‡ Westerman, Alvin E. .... Montgomery
†‡ Westerman, Fred C. .... Montgomery

SIBLEY COUNTY MEDICAL SOCIETY

Sibley County
Regular meetings, 3rd Monday of Odd number months
Annual meeting in November
Number of members 6

PRESIDENT
Schroeppel, John E. .... Winthrop
SECRETARY
Knoche, Harvey A. .... Gaylord
‡ Dysterheft, Adolf .... Gaylord
†‡ Greene, Gordon .... Cherokee, IA
Kath, Reinhard H. .... Arlington
Knoche, Harvey A. .... Gaylord
‡ Schroeppel, John E. .... Winthrop
Vener, John M. .... Arlington

SOUTHWESTERN MINNESOTA MEDICAL SOCIETY

Cottonwood, Jackson, Murray, Nobles, Pipestone and Rock Counties
Regular meetings first Monday of each month except July and August
Annual meeting, November
Number of members 60

PRESIDENT
Odlund, Donald M. .... Luverne
SECRETARY
Heiberg, O. M. .... Worthington
‡ Bader, Jean L. .... Slayton
‡ Basinger, Harold P. .... Windom
†‡ Basinger, Homer P. .... Windom
‡ Beckering, Gerrit .... Edgerton
‡ Beckering, Roland G. .... Edgerton
‡ Benjamin, Walter G. .... Pipestone
‡ Berner, Herbert W., Jr. .... Worthington
†‡ Bofenkamp, Ferdinand W. .... Luverne
‡ Boone, Ervin S. .... Luverne
‡ Boyd, Frank E. .... Pipestone
‡ Carlson, John V. .... Westbrook
‡ Carlson, Lloyd E. .... Worthington
‡ Christiansen, Harold A. .... Jackson
‡ Dahlquist, La Rue .... Pipestone
†‡ Daumann, Roy E. .... Minneapolis
‡ Dawson, Lorin D. .... Worthington
‡ Desai, B. J. .... Worthington
‡ Dokken, James H. .... Windom
‡ Doman, Victor W. .... Lakefield
‡ Eaton, David B. .... Worthington
‡ Faul, Bennie C. .... Worthington
‡ Fitch, Charles G. .... Worthington
‡ Glick, Dallas D. .... Mountain Lake
†‡ Halloran, Walter H. .... Jackson
‡ Halpern, David J. .... Brewster
‡ Harrison, Percy W. .... Worthington
‡ Hegstad, Thomas C. .... Windom
‡ Heiberg, O. M. .... Worthington
‡ Hoyer, Ludolf J. .... Oshkosh, WI
‡ Johnson, Alan R. .... Windom
‡ Keyes, Robert W. .... Pipestone
‡ Kilbride, Edwin A. .... Worthington
‡ Kotval, Russell J. .... Pipestone
‡ Laikola, Leslie A. .... Adrian
‡ Larsen, Russell H. .... Lakefield
‡ Lohmann, John G. .... Pipestone
‡ Maitland, Edwin T. .... Jackson
‡ Martin, Albert .... Luverne
‡ Minge, Raymond K. .... Worthington
‡ Nealy, Donald E. .... Adrian
‡ Nywall, Dean D. .... Slayton
‡ Odland, Donald M. .... Luverne
‡ Patterson, Hugh D. .... Slayton
‡ Pierce, Robert B. .... Heron Lake
‡ Pierson, Roy F. .... Slayton
†‡ Piper, William A. .... Mountain Lake
‡ Plucker, Milton W. .... Worthington
‡ Rud, Paul D. .... Luverne
‡ Ryding, Vincent .... Ames, IA
† Schade, Frederick .... Santa Cruz, CA
‡ Seisler, Edward P. .... Worthington
†‡ Sherman, Charles L. .... Luverne
‡ Siebert, Darrel W. .... Luverne
‡ Stam, John .... Worthington
‡ Strand, Jack W. .... Jasper
†‡ Stratte, Harold C. .... Windom
‡ Strough, Luverne C. .... Worthington
‡ Wells, Walter B. .... Jackson
‡ Wiens, Alvin L. .... Mountain Lake
†‡ Williams, Charles A. .... Seattle, WA

STEARNS-BENTON COUNTY MEDICAL SOCIETY

Stearns and Benton Counties
Regular meetings, third Thursday of each month
Annual meeting, January
Number of members 82

PRESIDENT
Autrey, William ... St. Cloud
SECRETARY
Espelien, Alan D. ... St. Cloud
SECRETARY, EXECUTIVE OFFICE
Kline, Mrs. Richard F. ... St. Cloud

	Alden, Charles W.	Sauk Rapids
	Asp, Donald S.	Milaca
	Aulick, Ernest J.	Paynesville
	Autrey, William A.	St. Cloud
‡	Bancroft, Burton R., Jr.	St. Cloud
	Barnett, Arthur	Foley
	Bauman, John C.	Foley
	Baumgartner, Florian H.	Albany
‡	Belshe, Joseph	St. Cloud
‡	Berger, Phil R.	St. Cloud
‡	Beuning, John B.	St. Cloud
‡	Bozanich, Milosh S.	St. Cloud
‡	Brattensborg, Henry J.	St. Cloud
‡	Brigham, Charles F., Jr.	St. Cloud
‡	Broker, Henry M.	St. Cloud
‡	Brown, Frank T.	St. Cloud
‡	Cesnik, Robert J.	Sauk Rapids
†‡	Clark, Harry B.	St. Cloud
*	Cleaves, Wm. D.	Sauk Centre
‡	Cumming, Robert J.	St. Cloud
	Donaldson, Charles S.	St. Cloud
	Dubois, Julian F.	Sauk Centre
‡	Espelien, Alan D.	St. Cloud
‡	Evans, Leslie M.	Sauk Rapids
‡	Gaida, Joseph B.	St. Cloud
‡	Gerstenkorn, George B.	Milaca
	Goehrs, Gilman H.	St. Cloud
	Grant, John C.	Sauk Centre
	Halenbeck, Philip L.	St. Cloud
	Harbaugh, John T.	St. Cloud
‡	Hedenstrom, Paul H.	Princeton
‡	Held, Wm. J.	St. Cloud
†	Henry, Clarence J.	Onamia
	Henry, Joseph E.	Milaca
‡	Higdon, Donald A.	St. Cloud
	Hughes, Bernard J.	St. Cloud
‡	Jaeger, Dwight E.	St. Cloud
‡	John, Byron L.	St. Cloud
	Johnson, Curtis A.	Princeton
‡	Johnson, William F.	St. Cloud
†‡	Jones, Richard N.	St. Cloud
‡	Keith, Paul J.	Milaca
‡	Kelly, James H.	St. Cloud
‡	Kelly, John F.	Cold Spring
‡	Koenig, Robert P.	St. Cloud
‡	Koop, Severin H., Jr.	St. Cloud
‡	Kruzich, Stephen J.	St. Cloud
	Kuhlmann, Lawrence B.	Melrose
	Kvistberg, Gerald K.	St. Cloud
	LaFond, Edward M.	St. Cloud
‡	Lenarz, Albert J.	St. Cloud
	Lindeman, Raymond J.	Paynesville
‡	Lindley, Stanley B.	St. Cloud
‡	Loeb, George L.	St. Cloud
‡	Loes, Louis A.	St. Cloud
†	McDowell, John P.	St. Cloud
	McNamara, John P.	Rice
‡	May, Robert B.	St. Cloud
†‡	Milhaupt, Emmett N.	Dunedin, FL
‡	Moran, Paul T.	St. Cloud
	Mueller, Rudolph B.	Richmond
‡	Murn, Thomas G.	St. Cloud
‡	Murray, Robert A., Jr.	St. Cloud
	Musachio, Nicholas F.	St. Paul
	Myre, Clifford R.	Paynesville
‡	Neils, Vernon E.	St. Cloud
	Nietfield, Aloys B.	Sauk Centre
‡	O'Keefe, James P.	St. Cloud
‡	Olinger, John N.	St. Cloud
‡	Petersen, Robert T.	St. Cloud
‡	Phares, Otto C.	St. Cloud
‡	Raetz, Sylvester J.	Maple Lake
	Rice, William H.	St. Cloud
	Richards, William B.	St. Cloud
‡	Ritchie, Donald A.	St. Cloud
‡	Rozycki, Anthony T.	St. Cloud
	Salk, Richard J.	Albany
	Savelkoul, Gene R.	Belgrade
	Schamber, Walter	St. Cloud
‡	Schmitz, Everett J.	St. Cloud
	Sisk, Harvey E.	St. Cloud
‡	Slanga, Roger A.	St. Cloud
	Stahn, Louis H.	St. Cloud
‡	Sommers, Stephen D.	St. Cloud
	Stiles, Clifford D.	Foley
‡	Thienes, R. Lawrence	St. Cloud
	Thuringer, Carl B.	St. Cloud
	Vanderpool, Thomas E.	Paynesville
	Van Nostrand, David M.	St. Cloud
‡	Veranth, Leonard A.	St. Cloud
‡	Wenner, Waldemar T.	St. Cloud
‡	Wittrock, Louis H.	Watkins
	Zachman, Albert H.	Melrose
‡	Zeleny, Joseph H.	St. Cloud

STEELE COUNTY MEDICAL SOCIETY

Steele County
Regular meetings, third Tuesday of every other month
Annual meeting, November
Number of members 26

PRESIDENT

	Lundquist, Curt W.	Owatonna

SECRETARY

	Arnesen, John F.	Owatonna
‡	Anderson, Franklin C.	Owatonna
	Arnesen, John F.	Owatonna
	Benjamin, Roger J.	Owatonna
‡	Buresh, Kenneth L.	Owatonna
‡	deWerd, Robert W.	Owatonna
	Dewey, Donald H.	Owatonna
†	Fischer, John R.	Creve Coeur, MO
‡	Floersch, Adrian J.	Owatonna
‡	Halvorsen, Daniel K.	Owatonna
	Hartung, Elmer H.	Claremont
‡	Henry, John C.	Owatonna
‡	Henry, Kenneth G.	Owatonna
‡	Hilker, Robert T.	Owatonna
	Honath, Donald H.	Owatonna
	Kulstad, Oscar S.	Dodge Center
	Linnell, Leonard S.	Owatonna
	Lundquist, Curt W.	Owatonna
	McEnaney, James E.	Owatonna
†	McIntyre, John A.	Owatonna
†	Morehead, Dewey E.	Bodega Bay, CA
	Nealy, Timothy E.	Blooming Prairie
‡	Olson, Albert J.	Owatonna
	Roberts, Oliver W.	Owatonna
†	Schaefer, Joseph F.	Owatonna
	Stransky, Theodore W.	Owatonna
†	Wilkowske, Rudolph J.	Owatonna

UPPER MISSISSIPPI MEDICAL SOCIETY

Aitkin, Cass, Crow Wing, Hubbard, Morrison, Todd & Wadena Counties
Regular meetings, January, April, September
Annual meeting, January
Number of members 78

PRESIDENT

	Kelley, Roger	Crosby

SECRETARY

	Anderson, Arden O.	Brainerd
‡	Aga, John H.	Brainerd
‡	Anderson, Arden O.	Brainerd
†	Anderson, Werner W.	Cincinnati, OH
*†‡	Badeaux, George I.	Brainerd
	Belcher, Royden A.	Little Falls
‡	Bender, James H.	Brainerd
‡	Bissinger, Lester L.	Brainerd
	Bolstad, Owen C.	Reno, NV
‡	Borgerson, Arthur H.	Long Prairie
‡	Brown, Russell T.	Browerville
	Burman, Richard E.	Aitkin
‡	Cardle, George E.	Brainerd
	Closuit, Frederick C.	Aitkin
‡	Coombs, Carl H.	Cass Lake
	Crow, Earl R.	Minnetonka
†	Davis, Lloyd T.	Wadena
	Davis, Luther F.	Wadena
‡	Dodson, Albertus F.	Brainerd
‡	Erickson, Alvin O.	Long Prairie
‡	Fitzsimons, William E.	Brainerd
	Fortier, George M. A.	Little Falls
‡	Gamm, Edgar R.	Park Rapids
†	Ghostley, Mary C.	Minneapolis
	Grimes, Paul T.	Park Rapids
‡	Grose, Frederick N.	Clarissa
	Halme, William B.	Wadena
	Hansen, Milo L.	Little Falls
	Haugen, Norman R.	Park Rapids
	Heid, James K.	Little Falls
‡	Johnson, Douglas L.	Little Falls
‡	Kanne, Earl R.	Brainerd
‡	Kelley, Roger E.	Crosby
	Knipp, William J.	Brainerd
‡	Knoll, W. V.	Brainerd
‡	Kussy, James C.	Little Falls
	Larson, Theodore G.	Brainerd
‡	Lee, Hubert W.	Brainerd
‡	Lelwica, Thaddeus J.	Staples
	Lofstrom, Dennis E.	Brainerd
	Longfellow, Helen W.	Brainerd
	Lund, Werner J.	Staples
‡	McLane, William O.	Brainerd
‡	Marshall, Clark M.	Crosby
‡	Marvin, Joseph E.	Brainerd
‡	Meller, Maurice	Brainerd
‡	Mennis, William I.	Staples
‡	Mortenson, Howard O.	Menahga
‡	Mosby, Maurice E.	Long Prairie
‡	Mulligan, Arthur M.	Brainerd
	Ness, Duane E.	Wadena
‡	Nixon, James B.	Crosby
	Nordlund, Mildred E.	Carmichael, CA
‡	O'Leary, John B.	Brainerd
	Olson, Lillian A.	Ah-Gwah-Ching
	Parker, Charles W.	Wadena
‡	Parker, Warren E.	Sebeka
‡	Pedersen, Robert L.	Brainerd
‡	Pelzl, Charles R.	Pine River
	Petraborg, Harvey T.	Aitkin
	Pettersen, George R.	Aitkin
‡	Poppie, Robert W.	Brainerd
‡	Reichelderfer, Charles F.	Staples
‡	Reichelt, Leland G.	Wadena
‡	Rhodes, Clinton E.	Park Rapids
‡	Ringle, Otto F.	Walker
‡	Scanlon, Hugh A.	Little Falls
†	Schulberg, Verne A.	Minneapolis
	Seifert, Donald R.	Little Falls
	Soriano, Dominador B.	Onamia
	Spieler, F. B.	Pequot Lakes
‡	Stein, Raymond J.	Pierz
‡	Stoy, Robert A.	Little Falls
	Vandersluis, Charles W.	Minneota
‡	Watson, Sidney W.	Little Falls
‡	Westley, Kent F.	Little Falls
‡	Wiger, Oliver E.	Little Falls
†	Will, William W.	Erskine
‡	Williams, Mervyn M.	Ah-Gwah-Ching
‡	Witter, Robert L.	Wadena

WABASHA COUNTY MEDICAL SOCIETY

Wabasha County
Regular meetings, special call
Annual meeting first Thursday after first Monday in October
Number of members 13

PRESIDENT

	Nehring, John	Wabasha

SECRETARY

	Gjerde, William P.	Lake City

‡	Bayley, E. Covell	Lake City
‡	Bouquet, Bertram J.	Wabasha
‡	Bowers, Robert N.	Lake City
‡	Ellis, Earl W.	Elgin
	Feigal, Gary R.	Lake City
‡	Gjerde, William P.	Lake City
†	Habein, Harold C.	Palo Alto, CA
‡	Mahle, Donald G.	Wabasha
‡	Martin, David E., III	Wabasha
	Martin, Doreen A.	Pepin, WI
†	Ochsner, Clarence G.	Santa Barbara, CA
†	Replogle, William H.	Eugene, OR
‡	Sontag, David W.	Lake City

WASECA COUNTY MEDICAL SOCIETY

Waseca County
Regular meeting, January
Annual meeting, January
Number of members 7

PRESIDENT

	Swenson, Orvie J.	Waseca

SECRETARY

	Olds, George H.	Waseca

‡	Cabot, Narcis P.	Waseca
	Davis, Raymond D.	Stockton, CA
‡	Hottinger, Raymond C.	Janesville
‡	Normann, Stephen T.	Waseca
‡	Oeljen, S. C. G.	Waseca
‡	Olds, George H.	New Richland
‡	Swenson, Orvie J.	Waseca

WASHINGTON COUNTY MEDICAL SOCIETY

Washington and Dakota Counties
Regular meetings, first Tuesday in each month
Annual meeting, June
Number of members 22

PRESIDENT

	Murphy, Thomas R.	Stillwater

SECRETARY

	Kiolbasa, Edward	Stillwater

‡	Bealka, Neil	Stillwater
†	Brabec, Paul F.	Hastings
‡	Canine, James L.	So. St. Paul
*‡	Carlson, Russel E.	Stillwater
	Chervenak, William A.	Marine-On-The-St. Croix
	Cowger, Robert C.	Farmington
‡	Dale, Les N.	Hastings
	deLeon, Ben	Stillwater
†	Eiden, Vera M.	Stillwater
	Fasbender, Herman T.	Hastings
†	Holcomb, Joel T.	Marine-on-the-St. Croix
	Hunter, Murray H.	Farmington
‡	Jenson, James E.	Stillwater
	Johnson, O. Guy	St. Paul
	Juergens, Manley F.	Stillwater
	Just, Herman J.	Hastings
‡	Kiolbasa, Edward B.	Stillwater
	Kulzer, Norbert J.	Hastings
‡	McCarten, Francis M.	Stillwater
	Midboe, Gilbert T.	Forest Lake
‡	Murphy, Thomas R.	Stillwater
	Peikert, Carl F.	Forest Lake
	Peterson, John O. H.	Hastings
*†	Poirier, Joseph A.	White Bear Lake
	Ruggles, George M.	Forest Lake
†‡	Sherman, Carnot H.	Bayport
‡	Stratte, Jon R.	Stillwater
*†‡	Stuhr, John W.	Stillwater
	Van Meier, Henry	Stillwater
	Weiss, Carl A.	Hastings
	Zeller, Hector	Hastings

WEST CENTRAL MINNESOTA MEDICAL SOCIETY

Big Stone, Pope, Stevens and Traverse Counties
Regular meetings, third Tuesday in March, May, September and November
Annual meeting, November
Number of members 24

	PRESIDENT	
	Zempel, Alan	Starbuck
	SECRETARY	
	Rossberg, Raymond A.	Morris
*‡	Arneson, Arthur I.	Morris
	Benjamin, Charles I.	Glenwood
†	Bergan, Otto	Clinton
‡	Brace, Ray I.	Clinton
‡	Bucher, Foster D.	Starbuck
‡	Christenson, Carl E.	Clinton
	Colago, Victor M.	Browns Valley
‡	Eide, O. A.	Hancock
	Hedemark, Homer H.	Ortonville
	Hedemark, Truman A.	Ortonville
‡	Karn, Jacob F.	Ortonville
	Knip, Robert J.	Ortonville
‡	Kolp, Berton A.	Glenwood
‡	Kooda, Jennings C.	Morris
‡	Kozel, William J.	Morris
‡	Lee, Gordon E.	Glenwood
‡	Magnuson, Allen E.	Wheaton
	Merrill, Robert	Des Moines, IA
‡	Popoff, Russel G.	Graceville
‡	Rossberg, Raymond A.	Morris
‡	Swedenburg, Paul A.	Glenwood
	Watson, Robert M.	Morris
‡	Winge, H. C.	Wheaton
‡	Zempel, Alan R.	Starbuck

WINONA COUNTY MEDICAL SOCIETY

Winona County
Regular meetings, second Tuesday in January, April, July and October
Annual meeting, January
Number of members 35

	PRESIDENT	
	Johnson, Curtis M.	Winona
	SECRETARY	
	Heise, Herbert vR.	Winona
	Andersen, Horace J.	Winona
‡	Boardman, Dalmon V.	Winona
	Brannick, Thomas L.	Winona
†	Christensen, Eli E.	Winona
‡	Degallier, Daniel	Winona
‡	Fenske, Arnold	Winona
‡	Finkelnburg, William	Winona
‡	Garber, George L.	Winona
‡	Haesly, Warren W.	Winona
‡	Hartwich, Roger F.	Winona
‡	Hawk, Dale J.	St. Charles
‡	Heise, Carl vR.	Winona
‡	Heise, Herbert vR.	Winona
‡	Heise, Paul vR.	Winona
	Heise, Philip vR.	Winona
‡	Heise, William vR.	Winona
‡	Hughes, Sidney O.	Winona
‡	Johnson, Curtis M.	Winona
‡	Johnston, Leonard	Winona
‡	Loomis, George L.	Winona
*†‡	McLaughlin, Edmund M.	Winona
‡	Mattison, Percy A.	Winona
†	Meinert, Albert E.	Winona
‡	Peterson, John R.	Rushford
‡	Roemer, Henry J.	Winona
‡	Rogers, Charles W.	Winona
‡	Schafer, Charles F.	Winona
†	Schmidt, Hilmer R.	Winona
	Testor, James V.	Winona
‡	Tweedy, John A.	Winona
‡	Tweedy, Robert B.	Winona
	Vollmer, Frederick J.	Winona
‡	Wilson, L. J.	Rushford
†‡	Wilson, R. H.	Lamoille
‡	Younger, Lewis I.	Winona

WRIGHT COUNTY MEDICAL SOCIETY

Wright County
Regular meetings, first Tuesday of every other month
Annual meeting in November
Number of members 16

	PRESIDENT	
	Sandeen, Robert M.	Buffalo
	SECRETARY	
	Maus, Donald J.	Monticello
‡	Anderson, Waldo P.	Buffalo
‡	Bendix, Lester H.	Annandale
‡	Catlin, Theodore J.	Buffalo
†‡	Ellison, Frank E.	Monticello
	Greenfield, W. Theodore	Champlin
‡	Guilfoile, Pierre J.	Delano
‡	Hart, William E.	Monticello
‡	Maus, Donald J.	Monticello
‡	Purves, G. Harland	Buffalo
‡	Sandeen, Robert M.	Buffalo
	Shin, Rok	Howard Lake
‡	Smorstok, Matthew B.	Monticello
‡	Steiner, Andrew M.	St. Michael
†‡	Thielen, R. D.	New Brighton
‡	Whitesell, L. A., Jr.	Buffalo
	Zapf, John D.	Monticello

ZUMBRO VALLEY MEDICAL SOCIETY

Olmsted, Houston, Fillmore and Dodge Counties
Regular meetings, first Wednesday of every odd-numbered month
Annual meeting, November
Number of members 882

PRESIDENT

Van Herik, Martin .... Rochester

SECRETARY

Doyle, James R. .... Rochester

EXECUTIVE SECRETARY

Fricke, Robert E. .... Rochester

‡ Aaro, Leonard A. .... Rochester
‡ Adson, Martin A. .... Rochester
‡ Affeldt, Daniel E. .... Kasson
† Ahlfs, Jacob J. .... Avon
‡ Ahmann, David L. .... Rochester
† Allen, Ray E. .... Rochester
# Aldrete, Joaquin S. .... Augusta, GA
Altenburg, Bernard M. .... Rochester
† Altman, Robert L. .... Rochester
† Amberg, Samuel .... Rochester
‡ Andersen, Howard A. .... Rochester
Anderson, Carl F. .... Rochester
†‡ Anderson, Mark J. .... Sun City, AZ
‡ Anderson, Markham J., Jr. .... Rochester
† Anderson, Michael D. .... Rochester
‡ Anderson, Milton W. .... Rochester
† Antlfinger, Thomas J. .... Rochester
† Arena, Paul J. .... Rochester
† Arkin, Charles L. .... Rochester
† Armbruster, Robert M. .... Rochester
† Arnold, Gordon B. .... Rochester
# Ashby, Thomas M. .... Decatur, GA
† Auger, Armand J. .... Rochester
Baars, Conrad W. .... Rochester
† Bachner, Irving N. .... Rochester
‡ Baggenstoss, Archie H. .... Rochester
Bahn, Robert C. .... Rochester
‡ Bair, Hugo L. .... Rochester
‡ Baird, Raymond L. .... Harmony
¶ Bajec, Dusan .... Belgrade, Yugoslavia
‡ Baker, George S. .... Rochester
† Baker, Harry R. .... Hayfield
‡ Baker, Hillier L., Jr. .... Rochester
† Baker, James A. .... Rochester
Balfour, William M. .... Lawrence, MO
Banfield, Frederick D. .... Rochester
‡ Banner, Edward A. .... Rochester
# Baran, Ernest M. .... Beaver Meadows, PA
† Barbee, Charles W., Jr. .... Rochester
†‡ Barker, Nelson W. .... Rochester
† Barnardo, David E. .... Rochester
†‡ Barnes, Arlie R. .... Rochester
‡ Barry, Maurice J., Jr. .... Rochester
‡ Bartholomew, Lloyd G. .... Rochester
‡ Bastron, James A. .... Rochester
† Baumgartner, Carl J., Jr. .... Rochester
‡ Bayrd, Edwin D. .... Rochester
‡ Beabout, John W. .... Rochester
‡ Beahrs, Oliver H. .... Rochester
Bean, Wm. J. .... Rochester
† Bechamps, Gerald J. .... Rochester
† Beckenbaugh, Robert D. .... Rochester
† Beckering, Raymond E. .... Rochester
† Beckley, James M. .... Rochester
‡ Belau, Paul G. .... Rochester
*† Benedict, William L. .... Rochester
‡ Bennett, Clayton J. .... Rochester
‡ Berge, Kenneth C. .... Rochester
† Bergh, Allen V. .... Rochester
†‡ Berkman, John M. .... Rochester
† Berman, Steven C. .... Rochester
‡ Bernatz, Philip E. .... Rochester
‡ Bianco, Anthony J., Jr. .... Rochester
‡ Bickel, William H. .... Rochester
† Bieger, R. Cyril .... Rochester
† Bigelow, Charles E. .... Dodge Center
‡ Bisel, Harry F. .... Rochester
‡ Black, B. Marden .... Rochester
Black, Leo F. .... Rochester
† Blune, Warren T. .... Rochester
† Boman, Peter L. .... Rochester
# Bonebrake, Robert A. .... Gurnee, IL
† Bosland, Jon H. .... Rochester
† Bowers, Frank R. .... Rochester
† Boyd, Allen S., Jr. .... Rochester
‡ Boyd, David A., Jr. .... Rochester
† Boyer, Stanley W. .... Rochester
† Braasch, William F. .... Rochester
# Brand, Frank R. .... Columbia, MO
‡ Brandenburg, Robert O. .... Rochester
† Breivis, James S. .... Rochester
† Brinkman, James F. .... Rochester
‡ Broadbent, James C. .... Rochester
‡ Brodhun, John C. .... Rochester
†‡ Brown, Alex E. .... Bradenton, FL
‡ Brown, Arnold L. .... Rochester
‡ Brown, Henry A. .... Rochester
‡ Brown, Joe R. .... Rochester
† Brown, Patrick M. .... Rochester
†‡ Brown, Philip W. .... Rochester
‡ Brown, Philip W., Jr. .... Rochester
† Brownfield, James A. .... Rochester
‡ Bryan, Richard S. .... Rochester
†# Bryar, George E. .... San Francisco, CA
† Bucchiere, John J., Jr. .... Rochester
† Buckley, John P. .... Rochester
† Buie, Louis A. .... Rochester
‡ Burbank, Mahlon K. .... Rochester
† Burge, Kelmar M., Jr. .... Rochester
‡ Burggert, E. O., Jr. .... Rochester
† Burgess, John N. .... Rochester
‡ Burich, Harry F. .... Rochester
‡ Burke, Edmund C. .... Rochester
‡ Burton, Robert C. .... Rochester
† Buscemi, Michael F. .... Rochester
† Bush, Stephen T. .... Rochester
‡ Butt, Hugh R. .... Rochester
† Cabanela, Miguel E. .... Rochester
‡ Cain, James C. .... Rochester
# Caldwell, Joseph G. .... Atlanta, GA
† Cali, Robert W. .... Rochester
‡ Callahan, John A. .... Rochester
† Camacho, Luis-Guillermo .... Rochester
‡ Campbell, Donald C. .... Rochester
‡ Campbell, Malcolm K. .... Rochester
† Carder, George A. .... Rochester
‡ Carlson, Harley C. .... Rochester
† Carnahan, Charles E. .... Rochester

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Zumbro Valley Medical Society *(Continued)*

	Carney, Francoise	Rochester
	Carr, David T.	Rochester
†	Carrington, Stewart G.	Rochester
‡	Carryer, Haddon M.	Rochester
†	Carter, David A.	Rochester
‡	Carter, Earl T.	Rochester
†	Cassan, Stanley M.	Rochester
#	Cecil, James W.	Marysville, CA
‡	Childs, Donald S., Jr.	Rochester
†	Ching, Ernesto	Rochester
†	Ching, Lily Tan	Rochester
†	Chiroff, Richard T.	Rochester
†	Chiu, Sylvester S.	Rochester
‡	Christensen, Norman A.	Rochester
†	Chulman, Miguel A.	Rochester
†	Chumbley, Lee C.	Rochester
‡	Clagett, O. Theron	Rochester
†	Clark, Edward C.	San Francisco, CA
†	Clark, Leslie W.	Manchester, IA
†	Clifton, Theodore A.	Hollywood, FL
‡	Code, Charles F.	Rochester
#	Coder, Donald M.	FPO, NY
‡	Cody, D. Thane	Rochester
†	Cohen, Manley	Rochester
‡	Colby, Malcolm Y., Jr.	Rochester
†	Coleman, Robert L.	Rochester
‡	Coles, Douglas T.	Rochester
†	Collins, Roger T.	Rochester
†	Collison, Robert W.	Rochester
†	Conn, Doyt L.	Rochester
†	Conn, Richard L.	Rochester
‡	Connolly, Daniel C.	Rochester
‡	Cook, Edward N.	Rochester
#	Cooper, Herbert A.	Beale AFB, CA
‡	Cooper, Talbert	Rochester
†	Cooperman, Avram M.	Rochester
‡	Corbin, Kendall B.	Rochester
#	Corcoran, James R.	Orange Park, FL
	Corrigan, Cyril J.	Rochester
†	Cotton, Gerald E.	Rochester
‡	Coventry, Markham B.	Rochester
†	Creasman, John P.	Rochester
#‡	Crowder, Bennett L., II	Ft. Campbell, KY
†	Culligan, David E.	Rochester
‡	Culp, Clyde E.	Rochester
‡	Culp, Ormond S.	Rochester
	Cupps, Roger E.	Rochester
‡	Dahlin, David C.	Rochester
‡	Dale, Allen J. D.	Rochester
†	Daniel, William W., Jr.	Rochester
†	Dankmyer, Frederick L.	Rochester
†	Daube, Jasper R.	Rochester
‡	Daugherty, Guy W.	Rochester
†	David, Ronald B.	Rochester
†	Davidson, Allan D.	Rochester
	Davignon, Jean	Montreal, Quebec
†	Davis, Austin C.	Pompano Beach, FL
‡	Davis, George D.	Rochester
‡	Dearing, William H.	Rochester
‡	Decker, David G.	Rochester
†	Deger, Grant E.	Rochester
†	DeMarco, Peter R.	Rochester
#	DeMordaunt, Paul R.	Blackfoot, ID
‡	DeRemee, Richard A.	Rochester
†	Detenbeck, Lee C.	Rochester
‡	Devine, Kenneth D.	Rochester
	Devloo, Robert A.	Rochester
‡	DeWeerd, James H.	Rochester
‡	Didier, Edward P.	Rochester
‡	Diessner, G. Roy	Rochester
	Dinapoli, Robert P.	Rochester
‡	Dines, David E.	Rochester
†	DiPasquale, Joseph A.	Rochester
†	Disney, Thomas F.	Rochester
‡	Divertie, Matthew B.	Rochester
*†	Dixon, Claude F.	Rochester
†	Dixon, George D.	Rochester
	Dobyns, James H.	Rochester
‡	Dockerty, Malcolm B.	Rochester
‡	Donoghue, Francis E.	Rochester
	Douglas, William W.	Rochester
‡	Douglass, Bruce E.	Rochester
‡	Doyle, James R.	Rochester
†	Dozois, Roger R.	Rochester
†	Drips, Della G.	Rochester
†	Dry, Thomas J.	Rochester
†	DuBois, David D.	Rochester
†	Dunn, Francis C., Jr.	Rochester
†	Dunn, Robert J.	Rochester
†	Duval, David L.	Rochester
	Duvoisin, George E.	Rochester
‡	Dyck, Peter J.	Rochester
‡	Dyer, John A.	Rochester
#	Echols, William J.	Selma, AL
#	Eckelberg, Merlyn E.	Ft. Clayton, Canal Zone
#	Edwards, Walter G., Jr.	Bethesda, MD
‡	Elkins, Earl C.	Rochester
‡	Ellis, F. Henry, Jr.	Rochester
†	El Shahawy, Mahfouz A.	Rochester
†‡	Emmett, John L.	Rochester
†	Emerson, Robert K.	Rochester
†	Emmons, W. Frank	Rochester
‡	Engel, Andrew G.	Rochester
†	Engelberg, Jerry	Rochester
‡	Erich, John B.	Rochester
‡	Erickson, Donald J.	Rochester
†	Errico, James M.	Rochester
†	Eselius, Erik P.	Rochester
‡	Espinosa, Raul E.	Rochester
†	Ettinger, David S.	Rochester
†	Evans, Titus C., Jr.	Rochester
*†	Evarts, Arrah B.	Rochester
†	Exarhos, Nicholas D.	Rochester
‡	Faber, John E.	Rochester
#‡	Facer, George W.	Millburg, OH
‡	Fairbairn, John F., II	Rochester
†	Farrell, Kenneth H.	Rochester
‡	Farrow, George M.	Rochester
‡	Faulconer, Albert, Jr.	Rochester
#	Fay, Thomas M.	Oakland, CA
†	Fehrenbaker, Lawrence G.	Rochester
†	Feinberg, Jack H.	Rochester
†	Feintuck, Theodore A.	Rochester
	Feldmann, Floyd M.	Pompano Beach, FL
†	Fenning, Robert L.	Rochester
‡	Ferguson, Richard H.	Rochester
‡	Ferris, Deward O.	Rochester
‡	Field, Charles A.	Rochester
†‡	Figi, Frederick A.	Rochester
†	Fina, Charles P.	Rochester
†	Finch, John E.	Rochester
†	Fink, Lawrence H.	Rochester
†	Finkelstein, Joel	Rochester
†	Fish, Charles R.	Rochester

Zumbro Valley Medical Society *(Continued)*

†	Fisher, Darrell E.	Rochester
†	Fritz, Frederick W.	Rochester
†	Flanigan, Donald J.	Rochester
†	Fluegel, John O.	Minneapolis
†	Flick, William F.	Rochester
#	Foley, Ralph B.	Ogden, UT
†	Foley, Thomas F.	Rochester
‡	Fontana, Robert S.	Rochester
†	Forker, Alan D.	Rochester
†	Foss, Edward L.	Condon, MT
†	Foster, David A.	Rochester
#	Foster, Thomas N., III	Whidbey Island, WA
‡	Foulk, William T., Jr.	Rochester
†	Fowler, Franklin S., Jr.	Rochester
#	Fox, John A.	Ft. Dix, NJ
†	Fraker, Keith E.	Rochester
#	Freel, Robert J.	Lackland AFB, TX
†	Freedman, Harvey M.	Rochester
‡	Frethem, Allen A.	Rochester
†	Fricke, Robert E.	Rochester
†	Fuller, Edwin B.	Rochester
†	Fulton, Richard E.	Rochester
†	Furlow, William L.	Rochester
†	Furman, Philip J.	Rochester
†	Furzyfer, Jacob	Rochester
	Galloway, Jackson R.	Alexandria, LA
†‡	Gambill, Carl M.	Rochester
‡	Gambill, Earl E.	Rochester
	Garber, James J.	Rochester
#	Garrick, James G.	Bethesda, MD
‡	Gastineau, Clifford F.	Rochester
†	Gau, Gerald T.	Rochester
‡	Gedge, Stafford W.	Rochester
†	Gentling, Peter A.	Rochester
‡	Geraci, Joseph E.	Rochester
†	Geshundheit, Sim	Rochester
*†	Giffin, Herbert Z.	Rochester
#	Gilbaugh, James H., Jr.	Eglin, FL
†	Gildersleeve, John W.	Rochester
†	Goldman, Sherwin	Rochester
#	Gisvold, John J.	APO San Francisco, CA
†	Gitnick, Gary L.	Rochester
†	Goellner, John R.	Rochester
†	Goldman, Sherwin	Rochester
†	Goldner, John C.	Rochester
‡	Goldstein, Norman P.	Rochester
‡	Goldston, Edgar	Rochester
‡	Gomez, Manuel R.	Rochester
‡	Good, C. Allen, Jr.	Rochester
†	Goodwin, Henry N.	Rochester
#	Goren, Hershel	APO San Francisco, CA
	Gorman, Columba A.	Rochester
‡	Gould, Allan B., Jr.	Rochester
†	Gould, Ronauld J.	Rochester
†	Gracey, Douglas R.	Rochester
†	Graf, John A.	Rochester
	Gravett, Desmond C.	Rochester
‡	Green, Paul A.	Rochester
†	Greenberg, Burton H.	Rochester
‡	Greene, Laurence F.	Rochester
‡	Gregg, James A.	Rochester
†	Griffiths, Robert W.	Rochester
#	Grimes, Allen E., Jr.	San Diego, CA
*†‡	Grindlay, John H.	Carbondale, CO
‡	Groover, Robert V.	Rochester
‡	Gross, John B.	Rochester
†	Gunderson, David H.	Rochester
†	Hable, Kathleen A.	Rochester
‡	Hagedorn, Albert B.	Rochester
‡	Hahn, Frederick W., Jr.	Rochester
‡	Hahn, Richard G.	Rochester
†‡	Haines, Samuel F.	Rochester
	Hall, Jack W.	Rochester
‡	Hallberg, Olav E.	Rochester
‡	Hallermann, Franz J.	Rochester
#	Ham, Oscar E., Jr.	San Antonio, TX
†	Hammargren, Lonnie L.	Rochester
†	Hammond, Hugh D.	Rochester
‡	Hanlon, David G.	Rochester
†	Hanash, Kamal A.	Rochester
†	Hanson, Jerome R.	Rochester
‡	Hanson, Norbert O.	Rochester
†	Harbold, Norris B., Jr.	Rochester
†	Hardy, Kent M.	Rochester
†‡	Hargraves, Malcolm M.	Rochester
†	Harrington, Stuart W.	Rochester
‡	Harris, Lloyd E.	Rochester
‡	Harrison, Edgar G., Jr.	Rochester
#	Hathaway, David S.	Arlington, VA
‡	Hartfield, James E., Jr.	Rochester
	Hartridge, Virginia B.	Rochester
†	Hastings, John D.	Rochester
†	Hatayama, Yoshiyuki	Rochester
†	Hauser, W. Allen	Rochester
†	Havig, Terrance A.	Rochester
‡	Hayles, Alvin B.	Rochester
†	Hayashi, Melvin M. K. W.	Rochester
#	Hays, James C.	APO New York
†	Heck, Frank J.	Rochester
†‡	Heidel, Werner	Cresskill, NJ
‡	Helmholz, Henry F., Jr.	Rochester
#	Henderson, Darrell L.	Portsmouth, VA
‡	Henderson, Edward D.	Rochester
	Henderson, John W.	Rochester
‡	Henderson, Lowell L.	Rochester
	Henke, Clarence E.	Rochester
‡	Hepper, Norman G.	Rochester
†	Herman, Peter S.	Rochester
‡	Hermans, Paul E,	Rochester
†	Hertzler, Jerrad J.	Rochester
†	Hewitt, Edith S.	Rochester
†	Hewitt, Richard M.	Rochester
‡	Higgins, John A.	Rochester
‡	Hill, John R.	Rochester
‡	Hill, Richard W.	Rochester
	Hines, Edgar A., Jr.	Brevard, NC
#	Hoagland, H. Clark	San Antonio, TX
‡	Hodgson, John R.	Rochester
†	Hoehn, James G.	Rochester
‡	Hoffman, David L.	Rochester
	Holbrook, Margaret A.	Rochester
	Holland, C. R.	Rochester
‡	Hollenhorst, Robert W.	Rochester
‡	Holley, Keith E.	Rochester
‡	Holman, Colin B.	Rochester
‡	Hoover, Norman W.	APO San Francisco, CA
†‡	Horton, Bayard T.	Rochester
‡	Howard, Frank M., Jr.	Rochester
‡	Howell, Llewelyn P.	Rochester
#	Hudgins, Robert L.	Ft. Logan, CO
†	Hudson, Albert W.	Rochester
‡	Huizenga, Kenneth A.	Rochester
†	Huerta, Enrique	Rochester
†	Hummer, William K.	Rochester

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Zumbro Valley Medical Society *(Continued)*

‡	Hunder, Gene G.	Rochester
†‡	Hunt, Arthur B.	Carmel, CA
‡	Hunt, James C.	Rochester
#	Hutchinson, James C., Jr.	Ft. Campbell, KY
†	Hynes, Kieran M.	Rochester
†	Iacobucci, Alfred P.	Rochester
†	Illig, William P.	Rochester
†	Isaacson, Ronald	Rochester
†	Isbell, Robert G.	Rochester
‡	Ivins, John C.	Rochester
‡	Jackman, Raymond J.	Rochester
†	Jaeger, John G.	Rochester
†	Janda, Wayne E.	Rochester
‡	Janes, Joseph M.	Rochester
†	Jensen, James W.	Rochester
†	Jereb, John A.	Rochester
‡	Johnson, Carl E.	Rochester
†	Johnson, Charles L.	Rochester
‡	Johnson, Einer W., Jr.	Rochester
†	Johnson, Gerhard J.	Rochester
†	Johnson, Kenneth A.	Rochester
†	Johnson, Thomas F.	Rochester
	Johnson, Ralph B.	Lanesboro
	Johnson, William J.	Rochester
†	Jones, Allen M.	Rochester
#	Jones, H. Royden, Jr.	APO New York, NY
#	Jordan, James J.	Great Lakes, IL
#	Joy, William B.	San Diego, CA
‡	Joyce, John W.	Rochester
‡	Judd, Edward S.	Rochester
†	Juttner, Hans-Udo	Rochester
‡	Kaese, Werner E.	Rochester
†	Kantack, Paul W.	Rochester
‡	Karnes, William E.	Rochester
†	Karsell, Philip R.	Rochester
†	Kasher, R. Jerome	Rochester
†	Kauderer, John G., Jr.	Rochester
‡	Kavanaugh, Gerald J.	Rochester
#	Katz, Elliott S.	Portsmouth, VA
‡	Kazmier, Francis J.	Rochester
†	Kearney, R. Wynn, Jr.	Rochester
‡	Kearns, Thomas P.	Rochester
‡	Keating, F. Raymond	Rochester
‡	Keith, Haddow M.	Rochester
†	Keith, Norman M.	Rochester
	Kelalis, Panayotis P.	Rochester
‡	Kelly, Patrick J.	Rochester
‡	Kempers, Roger D.	Rochester
‡	Kennedy, Charles C.	Rochester
†	Kennel, Arthur J.	Rochester
#	Kern, Eugene B.	Mission, KS
†‡	Kernohan, James W.	Rochester
‡	Kerr, Frederick W. L.	Rochester
#	Keys, Thomas F.	APO San Francisco, CA
‡	Kiely, Joseph M.	Rochester
‡	Kierland, Robert R.	Rochester
	Kimmel, George E.	Rochester
†	King, John E.	Rochester
‡	Kirby, Thomas J., Jr.	Rochester
	Kirklin, John W.	Birmingham, AL
	Klass, Donald W.	Rochester
#	Kline, Richard J.	Grand Forks, ND
‡	Knapp, Robert D., Jr.	Rochester
‡	Knutson, Lewis A.	Spring Grove
‡	Koelsche, Giles A.	Rochester
#	Kolb, Marvin O.	Ada
	Konicek, Robert G.	Rochester
†	Krigsten, Eli J.	Rochester
‡	Krupp, Neal E.	Rochester
†	Kruse, Robert L.	Rochester
†	Kubista, Theodore P.	Rochester
†	Kuers, Peter F. W.	Rochester
†	Kullmann, George L.	Rochester
†	Kuster, Gustavo G.	Rochester
‡	Kvale, Walter F.	Rochester
	Kvamme, Brynjulv	Mabel
‡	Kyle, Robert A.	Rochester
‡	Lake, Clifford F.	Rochester
†	Lantz, James P.	Rochester
†	La Point, Leon R.	Rochester
†	Larson, Richard H.	Rochester
#	Larson, Stephen L.	Keesler AFB, MS
#	Lattin, John E., III	El Paso, TX
†	Lavertu, Julien G.	Rochester
‡	Layton, Donald D., Jr.	Rochester
†	Leavelle, Dennis E.	Rochester
‡	Lee, Raymond A.	Rochester
‡	Lee, Robert E.	Rochester
†	Leech, Stephen H.	Rochester
‡	Leonard, Paul F.	Rochester
‡	Lillie, John C.	Rochester
	Lindsay, Malcolm I., Jr.	Rochester
‡	Linman, James W.	Rochester
‡	Linscheid, Ronald L.	Rochester
†	Lippman, Harry H.	Rochester
‡	Litin, Edward M.	Rochester
‡	Litzow, Thaddeus J.	Rochester
‡	Lofgren, Eric P.	Rochester
‡	Lofgren, Karl A.	Rochester
‡	Logan, George B.	Rochester
†	Love, J. Grafton	Rochester
	Ludes, Bernard F.	Rochester
‡	Lundborg, Richard O.	Rochester
‡	Lynn, Hugh B.	Rochester
‡	McBean, James B.	Rochester
†	McConahay, David R.	Rochester
‡	McConahey, William M., Jr.	Rochester
†	McDonald, Thomas J.	Rochester
†	McDuffie, Richard W., Jr.	Rochester
‡	McGill, Douglas B.	Rochester
‡	McGoon, Dwight C.	Rochester
‡	McIlrath, Donald C.	Rochester
†	McIlroy, Gary T.	Rochester
#	McKenna, Charles H.	Rochester
#	McKinne, Richard A.	Rochester
†	McLaughlin, Richard P.	Rochester
‡	MacCarty, Collin S.	Rochester
†	MacDonald, Charles J.	Rochester
†	MacDonald, Vance D.	Rochester
	MacLean, Alexander R.	Rochester
†‡	Magath, Thomas B.	Rochester
	Magid, Gail A.	Santa Cruz, CA
#	Magnant, Henry A.	Gallup, NM
†	Magnant, Claude D.	Rochester
†	Marion, Dennis F.	Rochester
†	Marion, Russell B.	Rochester
‡	Maher, Frank T.	Rochester
†	Mair, Douglas D.	Rochester
†	Malek, Reza S.	Rochester
‡	Malkasian, George D.	Rochester
‡	Mankin, Harold T.	Rochester
‡	Marcoux, J. Paul	Rochester
†	Margie, Robert P.	Rochester

Zumbro Valley Medical Society *(Continued)*

†	Marion, Dennis F.	Rochester
†	Marion, Russell B.	Rochester
†	Martalock, Dean L.	Rochester
‡	Martens, Theodore G.	Rochester
‡	Martin, Gordon M.	Rochester
‡	Martin, Harold R.	Rochester
‡	Martin, John T.	Rochester
‡	Martin, Maurice J.	Rochester
‡	Martin, William J.	Rochester
†	Martyn, David T.	Rochester
†	Masserman, Richard L.	Rochester
†	Masson, Duncan M.	Rochester
†	Masson, James C.	Rochester
‡	Masson, James K.	Rochester
#	Mastan, Peter F.	APO New York, NY
‡	Mathieson, Don R.	Rochester
†	Mattson, Roger A.	Rochester
#	Maupin, Roger A.	APO San Francisco, CA
	Mayne, John G.	Rochester
*†	Mayo, Charles W.	Rochester
†	Mejia-Diaz, Ivan A.	Rochester
†	Mekhjian, Hagop S.	Rochester
‡	Merritt, Wallace A.	Rochester
†	Mertens, Benny F.	Rochester
†	Mess, Charles F.	Rochester
	Messick, Joseph M., Jr.	Rochester
†	Meyerding, Henry W.	Rochester
†	Midyett, F. Allen	Rochester
†	Miller, Donald R.	Rochester
†	Miller, John W., Jr.	Rochester
‡	Miller, R. Drew	Rochester
‡	Miller, Ross H.	Rochester
‡	Millikan, Clark H.	Rochester
‡	Mills, Stephen D.	Rochester
†	Mitchell, John C., III	Rochester
#	Mockert, Thomas, Jr.	San Francisco, CA
†	Moeller, Henry G., Jr.	Torrance, CA
†	Moersch, Fred P.	Ft. Lauderdale, FL
†‡	Moersch, Herman J.	Rochester
‡	Moertel, Charles G.	Rochester
‡	Moffitt, Emerson A.	Rochester
†	Mohr, Armin A. A.	Rochester
‡	Molnar, George D.	Rochester
†‡	Montgomery, Hamilton	Rochester
†	Moore, Barry B.	Rochester
†	Moore, Daniel L.	Rochester
	Moore, Gordon L., II	Rochester
#	Morgan, Stephan S.	Chesapeake, VA
	Mori, Hideo	Grand Meadow
†	Morimoto, Allen M.	Rochester
‡	Morlock, Carl G.	Rochester
‡	Morrow, George W., Jr.	Rochester
	Morse, Robert M.	Rochester
†	Mulcahy, John J.	Rochester
‡	Mulder, Donald W.	Rochester
‡	Muller, Sigfrid A.	Rochester
†	Mullanax, Milton G.	Rochester
	Mussey, M. Elizabeth	Rochester
†	Myers, George H., Jr.	Rochester
‡	Myers, Thomas T.	Rochester
†	Nadeau, Claude	Trois-Rivieres, Que., Canada
	Nathan, David	Rochester
†	Nathan, Fred F.	Rochester
‡	Neault, Roger W.	Rochester
†	Nelson, Audrey M.	Rochester
	Nelson, J. Phillip	Rochester
†	Nettles, Joe L.	Rochester
†	Nguyen, Vu Van	Rochester
†	Nicholes, Karl R. K.	Rochester
‡	Nichols, Donald R.	Rochester
†	Nobrega, Fred T.	Rochester
†	O'Sullivan, Michael B.	Rochester
	Obetz, S. Wendell	Rochester
#	Odyniec, Norman A.	APO San Francisco, CA
†	Oels, Helen C.	Rochester
†	Okeson, Gyman C.	Rochester
†	Oldham, Robert L.	Rochester
†	Olive, John T.	Rochester
‡	Olsen, Arthur M.	Rochester
	Olson, Grant E.	West Concord
	Olson, Neal R.	Rochester
‡	Ongley, Patrick A.	Rochester
‡	Onofrio, Burton M.	Rochester
†	Onsgard, L. Kenneth	St. Petersburg, FL
†	Onstad, Thomas A.	Rochester
‡	Opitz, Joachim L.	Rochester
‡	Osmundson, Philip J.	Rochester
‡	Owen, Charles A., Jr.	Rochester
†	Oxman, Herbert A.	Rochester
†	Paarlberg, Donald	Rochester
†	Pacheco, Jose C.	Rochester
†	Pairolero, Peter C.	Rochester
‡	Palumbo, Pasquale J.	Rochester
‡	Paris, Jaime	Rochester
†	Parker, Joseph C., Jr.	Durham, NC
‡	Parker, Robert L.	Rochester
†	Parkhill, Edith M.	Rochester
‡	Parkin, Thomas W.	Rochester
‡	Paulson, John A.	Rochester
†	Payne, Robert A.	Rochester
‡	Payne, W. Spencer	Rochester
†	Pease, Gertrude L.	Rochester
‡	Perry, Harold O.	Rochester
‡	Peters, Gustavus A.	Rochester
	Petersen, Magnus C.	Rochester
	Peterson, Hamlet A.	Rochester
‡	Peterson, Lowell F. A.	Rochester
‡	Peyla, Thomas L.	Rochester
	Pierre, Robert V.	Rochester
†	Pingree, George C.	Rochester
†	Plummer, Alan L.	Rochester
†	Plummer, Leo J.	Rochester
†	Pluth, James R.	Rochester
	Polley, Howard F.	Rochester
‡	Pool, T. Lloyd	Rochester
†	Pool, Freidrich K.	Rochester
	Poston, Lawrence M.	Caledonia
‡	Pratt, Joseph H., Jr.	Rochester
†‡	Priestley, James T.	Rochester
†	Pritchard, Douglas J.	Rochester
	Pruitt, Raymond D.	Rochester
‡	Pugh, David G.	Rochester
‡	Pulec, Jack L.	Rochester
‡	Purnell, Don C.	Rochester
†	Raimundo, Hugo Sa	Rochester
‡	Ralston, Donald E.	Rochester
*†‡	Randall, Lawrence M.	Rochester
‡	Raymond, Randall	Rochester
†	Rawls, William E.	Houston, TX
†	Reckles, Lawrence N.	Rochester
†	Redfield, Nicholas P.	Rochester
	Reed, John H., Jr.	Salt Lake City, UT
‡	Reese, David F.	Rochester
#	Reeves, Bradford F.	Ft. Campbell, KY

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Zumbro Valley Medical Society *(Continued)*

†	Reid, Michael S.	Rochester
‡	Reiher, Jean	Rochester
†	Reilly, William F., Jr.	Rochester
†	Reiner, Carl E.	Rochester
‡	Reitemeier, Richard J.	Rochester
‡	ReMine, William H., Jr.	Rochester
‡	Restall, Charles J.	Rochester
	Rhoton, Albert L., Jr.	Rochester
	Riggs, B. Lawrence	Rochester
	Riley, Fenwick C.	Rochester
‡	Risser, Alden F.	Stewartville
	Ritter, Donald G.	Rochester
†	Rivers, Thomas A.	Rochester
	Robertson, Dennis M.	Rochester
†	Rodarte, Joe R.	Rochester
†	Rodman, Charles A., II	Rochester
‡	Rogne, William G.	Spring Grove
†	Roland, Charles, Jr.	Rochester
‡	Rome, Howard P.	Rochester
‡	Rooke, Edward D.	Rochester
#	Rosenbaum, Alan H.	Ft. Bragg, SC
‡	Rosenow, Edward C., III	Rochester
‡	Rosevear, John W.	Rochester
‡	Ross, James V., Jr.	Rochester
‡	Rovelstad, Randolph A.	Rochester
†‡	Rucker, Charles W.	Rochester
‡	Rushton, Joseph G.	Rochester
†	Russell, Rex D.	Rochester
#	Russell, Thomas J.	Barksdale, LA
†	Russell, Thomas, II	Rochester
†	Rydell, Ralph E.	Rochester
†‡	Rynearson, Edward H.	Rochester
#	Sabens, James A.	Ft. Campbell, KY
#	Sakulsky, Stephen B.	APO, San Francisco, CA
‡	Salassa, Robert M.	Rochester
	Sams, Wiley M., Jr.	Rochester
‡	Sanders, Frank V., Jr.	Rochester
‡	Sanderson, David R.	Rochester
†	Sandok, Burton A.	Rochester
†	Sanfelippo, Peter M.	Rochester
†	Santoscoy, Gilbert S.	Rochester
	Sauer, Robert L.	Preston
‡	Sauer, William G.	Rochester
†	Sato, Kazuyoshi	Rochester
†	Sauer, William G.	Rochester
‡	Sawtell, Robert R.	Rochester
	Sayre, George P.	Rochester
‡	Scanlon, Paul W.	Rochester
‡	Schattenberg, Thomas T.	Rochester
‡	Schirger, Alexander	Rochester
†	Schlein, Allen P.	Rochester
†	Schnur, Paul L.	Rochester
†	Schoen, Roland F., Jr.	Rochester
‡	Schoenfield, Leslie J.	Rochester
‡	Scholz, Donald A.	Rochester
	Schrantz, Robert D.	Rochester
†	Scotti, Angelo T.	Rochester
‡	Scudamore, Harold H.	Rochester
†	Sebald, John R.	Rochester
†	Sechas, Michael N.	Rochester
‡	Sedlack, Richard E.	Rochester
†	Sequra, Joseph W.	Rochester
‡	Seldon, Thomas H.	Rochester
†	Semerad, Emanuel	Rochester
†	Service, Frederick J.	Rochester
‡	Sessler, Alan D.	Rochester
†	Seybold, Marjorie E.	Rochester
†	Sheehan, William C.	Rochester
‡	Sheps, Sheldon G.	Rochester
†	Shertzer, John H.	Rochester
‡	Shick, Richard M.	Rochester
†	Shih, Cheh S.	Rochester
‡	Siekert, Robert G.	Rochester
†	Silverman, Louis F.	Houston, TX
‡	Silverstein, Murray N.	Rochester
‡	Simons, John N.	Rochester
‡	Simonton, Kinsey M.	Rochester
†	Simpson, Thomas E.	Rochester
†	Sisco, William T.	Rochester
	Skaug, Harold M.	Chatfield
†	Skaggs, Harold, Jr.	Rochester
†	Skinner, Ira C., III	Rochester
†	Skolnick, Judah L.	Rochester
‡	Slocumb, Charles H.	Rochester
#	Smith, David E.	APO, San Francisco, CA
†	Smith, Frederick L.	Rochester
*†	Smith, Harry L.	Rochester
‡	Smith, Lucian A.	Rochester
‡	Smith, Ralph E.	Rochester
‡	Smith, Reginald A.	Rochester
†	Snider, James H.	Rochester
†	Soderstrom, Carl W., Jr.	Rochester
†	Soltani, Jahanguir	Rochester
	Sones, Donald A.	Rochester
‡	Soule, Edward H.	Rochester
‡	Spencer, Robert J.	Rochester
‡	Spiekerman, Ralph E.	Rochester
†	Spil, Samuel	Rochester
‡	Spittell, John A., Jr.	Rochester
‡	Sprague, Randall G.	Rochester
#	Starkey, Thomas A.	Ft. Ord, CA
†‡	Stauffer, Maurice H.	Rochester
†	Stauffer, Richard N.	Rochester
#	Stecker, Raymond H.	APO, New York, NY
#	Stein, Paul S.	Waukegan, IL
†	Steinfeld, Carroll M.	Rochester
‡	Steinhilber, Richard M.	Rochester
#	Stenseth, Jon H.	APO, New York, NY
†	Sterling, William A.	Rochester
†	Stern, Barry L.	Rochester
†	Stevens, John C.	Rochester
#‡	Stewart, James R.	El Paso, TX
‡	Stickney, J. Minott	Rochester
‡	Stillwell, G. Keith	Rochester
‡	Stilwell, George G.	Rochester
‡	Stroebel, Charles F., Jr.	Rochester
	Strong, Cameron G.	Rochester
†	Stubbs, Samuel E.	Rochester
	Summerskill, William H.	Rochester
†	Suros, Juan	Rochester
†	Sutor, Anton H.	Rochester
‡	Svien, Hendrik J.	Rochester
†	Sutthiwan, Phaibul	Rochester
‡	Symmonds, Richard E.	Rochester
†	Svoboda, William B.	Rochester
†	Switz, Donald M.	Rochester
†	Tachovsky, Thomas J.	Rochester
†	Tancredi, Robert G.	Rochester
‡	Taswell, Howard F.	Rochester
	Tauxe, Welby N.	Rochester
†	Teem, Martin V., Jr.	Rochester
†	Theuerkauf, Frank J., Jr.	Rochester
	Thomas, Juergen E.	Rochester
#	Thompson, Dennis P.	China Lake, CA
†	Thompson, Gershom J.	Rochester
‡	Thurber, Deloran L.	Rochester

Zumbro Valley Medical Society *(Continued)*

†	Tilgner, Arthur D.	Rochester
†‡	Tillisch, Jan H.	Rochester
‡	Tinkham, Robert G.	Rochester
‡	Titus, Jack L.	Rochester
#	Todd, David W.	Kearny, NJ
†	Toft, Thomas V.	Rochester
	Tompkins, Richard B.	Rochester
†	Townsend, Gary L.	Rochester
	Trautmann, James C.	Rochester
†	Tsairis, Peter	Rochester
#	Turner, Eugene F.	Seattle, WA
†	Turner, Richard H.	Rochester
‡	Tyce, Francis A.	Rochester
†	Uihlein, Alfred	Rochester
‡	Underdahl, Laurentius O.	Rochester
‡	Utz, David C.	Rochester
†	Van Boxel, John A.	Rochester
	Van Dellen, Richard G.	Rochester
†	Van Dervoort, Robert L., Jr.	Rochester
	Van Herik, Martin	Rochester
#	Van Ness, W. Noel T.	Republic of Congo, Africa
‡	Vaughn, Louis D.	Rochester
†	Vandersteen, Paul R.	Rochester
†	Vargas-Cortez, Fernando	Rochester
	Verby, John E.	Bloomington
#	Vermillion, Stanley E.	Goldsboro, NC
†	Villanueva, Javier P.	Rochester
	Virnig, Hildegard J.	Caledonia
†	Vitas, Ovidio E.	Rochester
†	Vittands, Ingvars J.	Rochester
‡	Wagoner, Richard D.	Rochester
†	Wakim, Khalil G.	Rochester
‡	Wallace, Robert B.	Rochester
†	Waller, Robert R.	Rochester
#‡	Walls, Joseph T.	APO, New York, NY
†	Walsh, William E.	Rochester
†‡	Walters, Waltman	Rochester
‡	Ward, L. Emmerson	Rochester
	Washington, John A.	Rochester
†	Watkins, Charles H.	Sun City, AZ
#	Watkins, Phillip C.	Birmingham, AL
†	Webel, Max L.	Rochester
†	Weber, William F.	Rochester
†	Webster, Kirk H.	Rochester
‡	Weed, Lyle A.	Rochester
‡	Weeks, Richard E.	Rochester
†	Weick, James K.	Rochester
‡	Weidman, William H.	Rochester
†	Weier, Thomas E.	Rochester
†	Weiland, Louis H.	Rochester
	Weingart, Jon L.	Rochester
†‡	Weir, James F.	Rochester
†	Weisberg, Martin G.	Rochester
‡	Welch, John S.	Rochester
#	Wellek, Mark A.	APO, New York, NY
‡	Wellman, William E.	Rochester
	Wellner, Theodore O.	Rochester
‡	Wente, Harold A.	Rochester
†	West, Thomas L.	Rochester
†	Westbrook, Philip R.	Rochester
‡	Westrup, John E.	Lanesboro
	Wharton, William P.	Rochester
‡	Whisnant, Jack P.	Rochester
†	White, Roger D.	Rochester
†	White, Stewart A.	Rochester
†	White, William L.	Rochester
#	Whittaker, Lorin D., Jr.	Peoria, IL
†	Whyte, Thomas R.	Rochester
†	Wiegand, Stewart E.	Rochester
#	Wilber, Robert D.	Shawnee Mission, KS
#	Williams, David Eugene	Lehore, W. Pakistan
‡	Williams, Tiffany J.	Rochester
†	Williamson, Kenneth R.	Rochester
†‡	Willius, Fredrick A.	Rochester
†	Wilson, Charles S.	Rochester
†	Wilson, David F.	Rochester
‡	Wilson, Robert B.	Rochester
	Wilson, Viktor O.	Minneapolis
	Wiltsie, John C.	Rochester
†	Wilkowske, Conrad J.	Rochester
†	Winders, Robert E.	Rochester
‡	Winkelmann, Richard K.	Rochester
‡	Witten, David M.	Rochester
†	Wolpert, Enrique	Rochester
‡	Wollaeger, Eric E.	Rochester
	Wolochow, Donald A.	Rochester
	Wood, Lloyd T.	Rochester
†	Woods, John E.	Newtonville, MA
‡	Woolner, Lewis B.	Rochester
‡	Worthington, John W., Jr.	Rochester
†	Wotycha, Edward B.	Rochester
	Wychulis, Adam R.	Rochester
†	Wurtele, Lester H.	Rochester
†	Yackel, Douglas B.	Rochester
#	Yalowitz, Philip A.	San Diego, CA
‡	Yoss, Robert E.	Rochester
#	Youman, Joseph D., III	Salt Lake City, UT
‡	Young, Henry H.	Rochester
†	Zacharski, Leo R.	Rochester
†	Zimmerman. Bruce R.	Rochester

ALPHABETIC ROSTER

Key to Symbols

# Service
* Deceased
† Life, Associate, Affiliate and Resident
¶ Honorary

A

	Aaro, Leonard A.	Rochester
	Abraham, Arden L.	Duluth
	Abrams, Alexander, Jr.	St. Paul
	Abramson, Burton I.	Minneapolis
#	Abramson, Michael B.	Oakland, CA
	Abramson, Milton	Minneapolis
	Abullarade, Jose A.	Minneapolis
	Abuzzahab, Faruk S.	Minneapolis
	Adair, Albert F., Jr.	St. Paul
	Adams, Brandon L. W.	Minneapolis
	Adams, Harold R.	St. Paul
	Adams, Patrick J.	Shakopee
	Adams, Richard I.	Minneapolis
	Adcock, Leon L.	St. Paul
	Addy, Edward R.	Gilbert
	Adicoff, Arnold	Minneapolis
	Adkins, C. Douglas	Minneapolis
	Adkins, James T.	Coon Rapids
	Adson, Martin A.	Rochester
	Affeldt, Daniel E.	Kasson
	Aga, John J.	Brainerd
	Agustsson, Hreidar	Minneapolis
	Ahern, Eugene E.	Minneapolis
†	Ahlfs, Jacob J.	Avon
	Ahlstrom, Robert C.	Braham
	Ahmann, David L.	Rochester
	Ahola, Kenneth E.	Hibbing
	Ahrens, Curtis F.	Duluth
	Ahrens, Robert M.	St. Paul
	Akbar, Sajady	Minneapolis
	Akhaven, Traz	Alexandria
	Akins, Willard M.	Red Wing
	Aksoy, Mustafa	St. Paul
	Alari, Heino	Excelsior
	Albrecht, Raymond J.	St. Paul
	Alden, Charles W.	Sauk Rapids
	Alden, John F.	St. Paul
#	Aldrete, Joaquin S.	Augusta, GA
	Alexander, Harlan A.	Minneapolis
	Alexander, Paul J.	Hibbing
	Aling, Charles A.	Minneapolis
	Allen, James R.	Minneapolis
	Allen, John H.	Montevideo
†	Allen, Ray E.	Rochester
	Allison, David D.	Litchfield
†	Altenburg, Bernard M.	Rochester
	Alter, Milton	Minneapolis
†	Altman, Robert L.	Rochester
†	Altnow, Hugo O.	Coral Gables, FL
	Alton, Donald G.	St. Paul
	Amatuzio, Donald S.	Minneapolis
†	Amberg, Samuel	Rochester
	Amerongen, Werner W.	St. Paul
	Amra, Waleed	Chaska
	Amren, Don P.	Minneapolis
	Anderegg, Alfred F.	St. Paul
†	Andersen, Horace J.	Winona
	Andersen, Howard A.	Rochester
	Andersen, James G.	Minneapolis
	Andersen, Robert C.	Minneapolis
	Anderson, Arden O.	Brainerd
	Anderson, Arnold S.	Minneapolis
	Anderson, Carl F.	Rochester
	Anderson, Chester A.	Hector
	Anderson, Chester A.	Madison
	Anderson, David M.	Minneapolis
	Anderson, David P., Jr.	Austin
	Anderson, David W.	St. Paul
†	Anderson, Ernest R.	Minneapolis
	Anderson, Frank J.	Minneapolis
	Anderson, Franklin C.	Owatonna
	Anderson, Harold J.	Austin
	Anderson, James J.	St. Paul
	Anderson, James M.	Duluth
	Anderson, Jo E.	LeSueur
	Anderson, John A.	Minneapolis
	Anderson, John R.	Minneapolis
	Anderson, John W.	Blue Earth
†	Anderson, Karl W.	Excelsior
	Anderson, Margaret C.	St. Paul
†	Anderson, Mark J.	Sun City, AZ
	Anderson, Markham J., Jr.	Rochester
†	Anderson, Michael D.	Rochester
	Anderson, Milton W.	Rochester
	Anderson, Oscar D.	Mankato
†	Anderson, Richard E.	Willmar
	Anderson, Richard W.	St. Paul
	Anderson, Roger E.	Minneapolis
	Anderson, Roger L.	Minneapolis
	Anderson, Russell H.	Virginia
	Anderson, Thomas P.	Minneapolis
	Anderson, U. Schuyler	Edina
	Anderson, W. Robert	Minneapolis
	Anderson, Waldo P.	Buffalo
	Anderson, Wallace E.	Minneapolis
	Anderson, Wallace R.	Minneapolis
†	Anderson, Werner W.	Cincinnati, OH
	Anderson, William H.	Minneapolis
	Anderson, William T.	Minneapolis
	Andre, James C.	Minneapolis
†	Andreassen, Einar C.	Minneapolis
	Andreassen, Rolf L.	Minneapolis
	Andresen, Karl d'A	Minneapolis
	Ankner, Frank J.	Minneapolis
	Anonsen, Richard E.	Minneapolis
	Anselment, Lois A.	Excelsior
†	Antlfinger, Thomas J.	Rochester
†	Antolak, Stanley J., Jr.	St. Paul
†	Aquilina, Joseph N.	Mankato
	Antonelli, Jordan J.	Hibbing
†	Antonow, Arthur M.	Virginia
†	Arena, Paul J.	Rochester
†	Arends, Archabald L.	Minneapolis
	Arey, Stuart Lane	Minneapolis
	Arhelger, Stuart W.	Minneapolis

†	Arkin, Charles R.	Rochester
	Arlander, Clarence E.	Minneapolis
	Arlander, Thomas R.	Minneapolis
	Arling, Leonard S.	Minneapolis
†	Armbruster, Robert M.	Rochester
	Arms, James J.	Minneapolis
	Armstrong, Byron H.	Minneapolis
	Armstrong, Ralph S.	Winnebago
†	Arndt, Harry W.	Detroit Lakes
	Arnesen, John F.	Owatonna
	Arnesen, Paul M.	Mankato
*	Arneson, Arthur I.	Morris
†	Arnold, Ann W.	Minneapolis
†	Arnold, Gordon B.	Rochester
	Arnold, Thomas B.	Minneapolis
	Arny, Frederick P.	St. Paul
	Aruguete, Alayne	Sandstone
	Aruguete, Jose	Sandstone
	Arzt, Philip K.	St. Paul
#	Ashby, Thomas M.	Decatur, GA
	Ashmore, Herbert C.	St. Paul
	Asp, Donald S.	Milaca
	Asta, Joseph J.	Duluth
†	Athens, Alvin G.	Santa Barbara, CA
	Atmore, William G.	Duluth
	Aufderheide, Arthur C.	Duluth
†	Auger, Armand J.	Rochester
	Aughenbaugh, John W.	Minneapolis
	Aulick, Ernest J.	Paynesville
	Auran, David B.	St. Paul
	Aurelius, J. Richards	St. Paul
	Ausman, Duane R.	St. Paul
†	Aust, John C.	Minneapolis
	Austrian, Sol	St. Paul
	Autrey, William A.	St. Cloud
	Avant, Robert F.	Minneapolis
	Azad, A. M.	Minneapolis

B

	Baab, Robert O.	Crookston
	Baars, Conrad W.	Rochester
	Babb, Frank S.	St. Paul
	Bach, Jerome M.	Minneapolis
†	Bachner, Irving N.	Rochester
	Backus, Byron C.	Cloquet
	Backus, Lloyd B.	Cloquet
	Backus, Reno W.	Nopeming
*†	Badeaux, George I.	Brainerd
	Bader, J. L.	Slayton
	Baggenstoss, Archie H.	Rochester
	Baggenstoss, Osmond J.	Minneapolis
	Bagley, Charles M.	Duluth
	Bagley, Elizabeth C.	Duluth
	Bagley, Russell W.	Minneapolis
	Bah, Merle C.	St. Paul
	Bahn, Robert C.	Rochester
	Baich, Velemir M.	Coleraine
	Bair, Hugo L.	Rochester
	Baird, Raymond L.	Harmony
¶	Bajec, Dusan	Poljane, Yugoslavia
†	Baken, Melvin P.	Minneapolis
	Baken, Melvin P., Jr.	Minneapolis
	Baker, Abe B.	Minneapolis
	Baker, C. Camak	Minneapolis
	Baker, Chilton R., Jr.	St. Paul
	Baker, Daniel R.	Anoka
	Baker, George S.	Rochester
†	Baker, Harry R.	Hayfield
	Baker, Hillier L., Jr.	Rochester
†	Baker, James A.	Rochester
	Baker, Jeannette L.	Fergus Falls
	Baker, Milton E.	Minneapolis
	Baker, Norman H.	Fergus Falls
	Bakke, Arnold C.	Minneapolis
	Bakkila, Henry E.	Duluth
	Balce, Regino V.	St. Paul
	Balderson, Robert P.	Grand Rapids
	Balfour, William M.	Lawrence, KS
	Balkin, Samuel G.	Minneapolis
	Balkins, John W.	Minneapolis
	Balmer, Albert I.	Duluth
	Balogh, Charles J.	Minneapolis
	Bancroft, Burton R., Jr.	St. Cloud
	Bandt, Calvin M.	Minneapolis
	Banfield, Frederick	Rochester
†	Bank, Harry E.	Minneapolis
	Banner, Edward A.	Rochester
	Banovetz, John D.	Minneapolis
	Baraga, Anthony R.	Hibbing
#	Baran, Ernest M.	Beaver Meadows, Pa.
	Barbarisi, Charles F.	Mankato
†	Barbee, Charles W., Jr.	Rochester
	Barber, Tracy E.	Austin
*	Bardon, Richard	Duluth
	Barker, John D.	Duluth
*†	Barker, Nelson W.	Rochester
†	Barnardo, David E.	Rochester
†	Barnes, Arlie R.	Rochester
	Barnes, Richard E.	Aurora
	Barnett, Arthur J.	Foley
	Barnett, Robert M.	Minneapolis
†	Barney, Leon A.	Duluth
	Barno, Alex	Minneapolis
	Barr, Lowell C.	Albert Lea
	Barr, Lowell W.	Albert Lea
	Barr, Maxwell M.	Minneapolis
	Barr, Robert N.	Minneapolis
	Barrett, Earl E.	Duluth
	Barrett, Patrick J.	Minneapolis
	Barron, Jesse J.	Minneapolis
†	Barron, Mosses	Beverly Hills, CA
	Barry, George J.	Minneapolis
	Barry, Maurice J., Jr.	Rochester
	Bart, Bruce J.	Minneapolis
	Bartholdt, H. Peter	Cook
	Bartholomew, Lloyd G.	Rochester
	Bartness, John E.	Albert Lea
	Bartzen, Peter J.	Duluth
	Basinger, Harold P.	Windom
†	Basinger, Homer P.	Windom
	Bastron, James A.	Rochester

	Batdorf, B. Niles	Mankato
	Bateman, Clarence V.	Fergus Falls
	Bauer, Eugene L.	St. Paul
	Bauer, Paul G.	Faribault
	Bauman, John C.	Foley
†	Baumgartner, Carl J., Jr.	Rochester
	Baumgartner, Florian H.	Albany
	Bayley, E. Covell	Lake City
	Bayrd, Edwin D.	Rochester
	Beabout, John W.	Rochester
	Beach, Northrop	Minneapolis
	Beahrs, Oliver H.	Rochester
	Bealka, Neil M.	Stillwater
	Bean, Charles N.	Waconia
†	Bean, William J.	Rochester
	Beard, Archibald H., Jr.	Minneapolis
	Beaton, J. Gordon	Northfield
†	Bechamps, Gerald J.	Rochester
	Beck, Charles J.	No. St. Paul
†	Beckenbaugh, Robert D.	Rochester
†	Becker, Arnetta M.	Treasure Island, FL
	Becker, Frederic T.	Duluth
	Beckering, Gerrit	Edgerton
†	Beckering, Raymond E.	Rochester
	Beckering, Roland G.	Edgerton
†	Beckley, James M.	Rochester
	Becklund, Roger W.	Minneapolis
	Beckman, Donovan L.	St. Paul
	Beek, Harvey O.	St. Paul
	Beeman, John A.	Minneapolis
	Beer, John J.	St. Paul
	Behr, Orlo K.	Crookston
	Beirstein, Samuel	Minneapolis
	Beiswanger, Richard H.	Minneapolis
	Belau, Paul G.	Rochester
	Belcher, Royden A.	Little Falls
	Bell, Donald C.	Minneapolis
	Bell, Harry M., Jr.	Duluth
	Bellomo, James	St. Paul
	Bellomo, John	Fairmont
	Bellville, Titus P.	Minneapolis
	Belshe, Joseph	St. Cloud
	Belsito, Alphonso A.	St. Paul
	Belz, Reinmar	St. Paul
	Belzer, Meyer S.	Minneapolis
	Bendel, William L., Jr.	Minneapolis
	Bendel, Richard P.	Minneapolis
	Bender, James H.	Brainerd
	Bendix, Lester H.	Annandale
*†	Benedict, William L.	Rochester
†	Benell, Otto E.	Britt
	Benepe, James L.	St. Paul
	Benesh, Louis A.	Minneapolis
	Benjamin, Charles I.	Glenwood
	Benjamin, Edwin G.	Minneapolis
	Benjamin, Harold G.	Minneapolis
	Benjamin, Richard D.	Minneapolis
	Benjamin, Robert B.	Minneapolis
	Benjamin, Roger J.	Owatonna
	Benjamin, Walter G.	Pipestone
	Bennett, Clayton J.	Rochester
*	Benson, A. H.	Little Falls
	Benthack, Elaine M.	Minneapolis
	Bentz, Herman D.	Anoka
	Bepko, Marie K. (Mrs. Puumala)	Cloquet
*†	Berdez, George L.	Duluth
	Berestka, Stephen J.	Minneapolis
	Berg, Arnold M.	Thief River Falls
	Berg, Clinton C.	Excelsior
†	Bergan, Otto	Clinton
	Bergan, Robert O.	Duluth
	Berge, Harry L.	Mora
	Berge, Kenneth G.	Rochester
	Berger, Alex G.	Minneapolis
	Berger, Phil R.	St. Cloud
†	Bergh, Allen V.	Rochester
	Bergh, George S.	Minneapolis
	Bergh, Solveig M.	Minneapolis
	Berglund, Alvin E.	Cambridge
	Berglund, Eldon B.	Minneapolis
*†	Bergman, Oscar B.	St. James
	Bergquist, James R.	Minneapolis
†	Bergstrom, Ralph W., Jr.	Minneapolis
†	Bergstrom, William J.	Minneapolis
	Berkman, D. S	Willmar
†	Berkman, John M.	Rochester
	Berkwitz, Nathaniel J.	Minneapolis
	Berman, David A.	Minneapolis
	Berman, Reuben	Minneapolis
†	Berman, Steven C.	Rochester
	Bernatz, Philip E.	Rochester
	Berner, Herbert W., Jr.	Worthington
†	Bernier, Merrill J.	No. St. Paul
	Bernstein, Dorothy M.	Minneapolis
	Bernstein, Eugene F.	Minneapolis
	Bernstein, Irving C.	Minneapolis
†	Bernstein, William C.	St. Paul
	Berris, Harold	Minneapolis
	Berry, Ronald N.	Minneapolis
	Berzins, Rainis	Minneapolis
†	Bessesen, Alfred N.	Minneapolis
	Beuning, John B.	St. Cloud
	Bevis, William D.	Minneapolis
	Bhattacharyya, Sisir K.	Battle Lake
†	Bianco, Anthony J.	Duluth
	Bianco, Anthony J., Jr.	Rochester
	Bickel, William H.	Rochester
	Bickford, Joyce A.	Rochester
†	Bieger, R. Cyril	Rochester
	Bieter, Raymond N.	Minneapolis
	Bieter, Thomas G.	St. Paul
*†	Bigelow, Charles E.	Dodge Center
	Bigler, Earl E.	Perham
	Bigler, Ivan E.	Perham
	Bilgutay, Aydin M.	Minneapolis
	Bilka, Paul J.	Minneapolis
	Billings, Harry H.	Red Wing
	Billman, Herbert R.	Minneapolis
	Binder, Manuel R.	Minneapolis
*†	Binet, Henry E.	Grand Rapids
	Bingham, George C.	Olivia
#	Birkebak, Roland C.	St. Paul
#	Birkemeyer, Eugene J.	Mountain Home AFB, ID
	Birkey, Thomas G.	Montevideo
	Bisel, Harry F.	Rochester
	Bissinger, Lester L.	Brainerd
	Bittick, Wilbur H.	Minneapolis
	Black, B. Marden	Rochester
	Black, Earl J.	White Bear Lake
	Black, Leo F.	Rochester
	Black, William A.	New Ulm
	Blackard, Clyde E.	Minneapolis
	Blackburn, Henry W., Jr.	St. Paul
	Blackwell, Leonard H.	Hutchinson
	Blake, Allan J.	Hopkins
	Blake, James A.	Hopkins

	Blake, Paul S.	Minneapolis
	Bloch, Henry S.	Minneapolis
	Bloedel, Traugott J.	Osseo
	Blomberg, Robert D.	Minneapolis
	Blomberg, William R.	St. Paul
	Bloom, David	Minneapolis
	Bloom, Joseph	Silver Bay
	Bloom, Norman B.	Minneapolis
	Blumberg, Henry B.	St. Paul
	Blumenthal, Malcolm N.	Minneapolis
	Blumer, Arlo R.	Albert Lea
	Blune, Warren T.	Rochester
	Boardman, Dalmon V.	Winona
	Boardman, Peter J.	Wayzata
	Boardman, William J.	Minneapolis
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	Boecker, Bernhard	Duluth
	Bofenkamp, Benjamin	Minneapolis
†	Bofenkamp, Ferdinand W.	Luverne
	Bohn, Donald G.	Minneapolis
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	Boies, Lawrence R., Jr.	St. Paul
	Boline, Clifford A.	Battle Lake
	Bologna, Camillo V.	Moorhead
	Bolstad, Owen C.	Reno, NV
	Bolt, Donald A.	Minneapolis
	Bolz, J. Arnold	Grand Rapids
	Boman, Paul G.	Duluth
†	Boman, Peter L.	Rochester
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	Bonello, Frank J.	St. Paul
	Bonner, John L.	Grand Rapids
	Boody, George	Cambridge
	Boone, Ervin S.	Luverne
	Borgerson, Arthur H.	Long Prairie
	Borgerson, M. A.	Hanley Falls
	Borman, Chauncey N.	Minneapolis
	Borowicz, Leonard A.	Minneapolis
	Bosland, Howard G.	Willmar
†	Bosland, Jon H.	Rochester
	Bosley, Patrick	Balaton
†	Bottolfson, B. T.	Moorhead
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	Bouquet, Bertram J.	Wabasha
	Bouthilet, Florence J.	Minneapolis
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	Bowers, Gordon	Minnetonka
	Bowers, Robert N.	Lake City
	Bowlin, Paul F.	Minneapolis
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	Boyd, David A., Jr.	Rochester
	Boyd, Frank E.	Pipestone
	Boyer, Samuel H.	Duluth
†	Boyer, Stanley W.	Rochester
	Boyle, Francis J.	Springfield
†	Boynton, Ruth E.	Miami, FL
†	Boysen, Herbert	Madelia
	Boyum, Allan J.	Marshall
	Bozanich, Milosh S.	St. Cloud
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†	Brabec, Paul F.	Hastings
	Brace, Ray I.	Clinton
	Bradley, Jeanne B.	Minneapolis
	Bradley, John G.	Minneapolis
	Brady, Charles H., Jr.	Mankato
	Brainerd, John B.	St. Paul
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	Brandenburg, Robert O.	Rochester
	Brandt, Henry E.	Minneapolis
†	Branham, Donald S.	Hastings
	Brannick, Thomas L.	Winona
	Bransford, Paul W.	Minneapolis
	Bratholdt, James W.	Watertown
†	Bratrud, Edward	Alexandria
†	Bratrude, Earl J.	Hopkins
	Brattensborg, Henry J.	St. Cloud
	Brauer, William W.	Minneapolis
	Braun, Ohrmundt C.	Grand Rapids
	Braun, Rene	Minneapolis
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	Bray, Jerome L.	Thief River Falls
†	Breivis, James S.	Rochester
	Breitenbucher, Robert B.	Minneapolis
	Brekke, Harvey J.	Minneapolis
	Brende, Joel O.	Littlefork
	Brenk, Paul E.	Detroit Lakes
	Brennan, Joseph G.	Minneapolis
	Brettingen, Larry J.	Mora
	Bretzke, Carl O.	Hutchinson
	Briggs, John F.	St. Paul
	Briggs, Thomas G.	White Bear Lake
	Brigham, Charles F., Jr.	St. Cloud
	Brill, Alice K.	Minneapolis
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	Brink, Donald M.	St. Peter
†	Brinkman, James F.	Rochester
	Briones, Bienvenido R.	Hopkins
	Broadbent, James C.	Rochester
	Broadie, Thomas E.	St. Paul
	Brockway, Roger W.	Grand Rapids
	Brodhun, John C.	Rochester
†	Brodie, Walter D.	St. Paul
	Broker, Henry M.	St. Cloud
	Broman, Harold R., Jr.	No. St. Paul
	Brooker, Warren J.	Duluth
†	Brooks, Charles N.	Wayzata
†	Brown, Alex E.	Brandenton, FL
	Brown, Arnold L.	Rochester
	Brown, Charles T.	St. Paul
#	Brown, Christopher J.	Mineral Wells, TX
	Brown, Cyrus C., Jr.	Duluth
	Brown, Frank T.	St. Cloud
	Brown, Glenn W.	Halstad
	Brown, Hector M.	St. Paul
	Brown, Henry A.	Rochester
	Brown, James E., Jr.	St. Paul
	Brown, James P.	St. Paul
	Brown, Joe R.	Rochester
	Brown, John H.	Minneapolis
	Brown, John M.	St. Paul
†	Brown, Patrick M.	Rochester
†	Brown, Philip W.	Rochester
	Brown, Philip W., Jr.	Rochester
	Brown, Russell T.	Browerville
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	Brown, William D., Jr.	Minneapolis
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	Bruhl, Heinz H.	Faribault
†	Brusegard, James F.	Red Wing
	Bryan, Richard S.	Rochester
#	Bryar, George E.	San Francisco, CA
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	Bucher, Foster D.	Starbuck
	Buchstein, Harold F.	Minneapolis
†	Buck, Frederick H.	Shakopee
†	Buckley, John P.	Rochester

	Buckley, Joseph J.	Minneapolis
	Buckley, Robert P.	Duluth
	Buesgens, Ralph H.	Waterville
	Bugby, Robert D.	Minneapolis
	Bugenstein, Robert H.	Minneapolis
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	Buie, Louis A., Jr.	Minneapolis
	Bulinski, Theodore J.	St. Paul
	Bulluck, Matthew H.	Duluth
	Bundt, Robert E.	Minneapolis
	Bunker, Bevan W.	Anoka
	Buran, David J.	Minneapolis
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	Burchell, Howard B.	Minneapolis
	Buresh, Kenneth L.	Owatonna
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	Burgert, E. O., Jr.	Rochester
	Burgess, John N.	Rochester
	Burich, Harry F.	Rochester
	Burke, Edmund C.	Rochester
	Burkholder, Dayton D.	Anoka
	Burklund, Edwin C.	St. Paul
	Burlingame, David A.	St. Paul
	Burman, Richard E.	Aitkin
	Burmeister, Richard O.	St. Paul
	Burnett, Joseph W.	New Ulm
	Burnham, Wesley H.	Minneapolis
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	Burns, John M.	St. Paul
†	Burns, M. A.	Milan
	Burseth, Edgar C.	Mora
	Burton, J. Richard	St. Paul
	Burton, Robert C.	Rochester
	Burton, Thomas P.	Minneapolis
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	Bush, Robert P.	St. Paul
†	Bush, Stephen T.	Rochester
	Butler, John K.	Cloquet
	Butt, Hugh R.	Rochester
†	Butzer, John A.	Mankato
	Byrne, William J.	St. Paul

C

†	Cabanela, Miguel E.	Rochester
	Cable, Morris L.	Minneapolis
	Cabot, Clyde M.	Minneapolis
	Cabot, Narcis	Waseca
	Cain, Clark L.	St. Paul
	Cain, James C.	Rochester
	Cain, James H.	Alexandria
	Cairns, Robert J.	Redwood Falls
#	Caldwell, Joseph G.	Atlanta, GA
†	Calhoun, Frank W.	Albert Lea
†	Cali, Robert W.	Rochester
	Calin, S. Hartley	Minneapolis
	Callahan, John A.	Rochester
†	Camacho, Luis-Guillermo	Rochester
†	Cameron, Isabell L.	Minneapolis
	Cameron, John H.	Clovis, NM
	Camp, Ray J.	Madison
	Campaigne, Robert J.	Duluth
	Campbell, Denis V.	Minneapolis
	Campbell, Donald C.	Rochester
	Campbell, John C.	Albert Lea
	Campbell, Malcolm K.	Rochester
	Campbell, Orwood J.	Minneapolis
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	Cant, Wilbur F.	Red Wing
†	Cantwell, William F.	International Falls
	Caplan, Leslie	Minneapolis
	Card, William H.	Minneapolis
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	Cardle, George E.	Brainerd
	Cardle, James G.	Minneapolis
	Cardle, John B.	Minneapolis
	Carey, James B., Jr.	Minneapolis
	Carey, Lewis S.	St. Paul
	Carlander, Lester W.	Minneapolis
	Carley, Richard B.	St. Paul
	Carlon, Donald L.	Moorhead
	Carlson, Carl E.	Alexandria
	Carlson, Charles V.	Mound
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	Carlson, Harley C.	Rochester
	Carlson, Homer J.	Pelican Rapids
	Carlson, John V.	Westbrook
	Carlson, Lawrence	Minneapolis
	Carlson, Lloyd E.	Worthington
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	Carlson, Vernon J.	Moorhead
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	Carney, Francoise	Rochester
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	Carr, David T.	Rochester
	Carr, William J.	Minneapolis
	Carrier, Thomas C.	Minneapolis
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	Carryer, Haddon M.	Rochester
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	Carter, Earl T.	Rochester
	Carthey, Frank J.	New Ulm
	Caspers, Carl G.	Minneapolis
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	Catlin, Theodore J.	Buffalo
	Cauble, Charles F.	Minneapolis
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	Cavert, H. Mead	Minneapolis
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	Cedarleaf, Cherry B.	White Bear Lake
	Ceder, Elmer T.	Minneapolis
	Cella, Joseph A.	Minneapolis
	Ceplecha, Stanley F.	Redwood Falls
	Cervenka, Charles F.	New Prague
	Cesnik, Robert J.	Sauk Rapids
	Chadbourn, Wayne A.	Minneapolis
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	Challman, S. Alan	Minneapolis
#	Chandler, William M.	Great Lakes, IL

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	Chedister, Charles R.	Minneapolis
	Chermak, Francis G.	Phoenix, AZ
	Chervenak, William A.	Marine-on-St. Croix
	Chesler, Merrill D.	Minneapolis
	Child, Sherman B.	Minneapolis
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	Childs, Donald S., Jr.	Rochester
†	Ching, Ernesto	Rochester
†	Chiroff, Richard T.	Rochester
	Chisholm, Tague C.	Minneapolis
†	Chiu, Sylvester Shin-Yat	Rochester
	Chou, Shelley N.	Minneapolis
	Christensen, Clarence H.	Duluth
†	Christensen, Eli E.	Winona
	Christensen, Llewellyn E.	Minneapolis
	Christensen, Norman A.	Rochester
	Christenson, Carl E.	Clinton
	Christenson, Leland R.	Maple Plain
	Christgau, Roger A.	Minneapolis
	Christian, William L.	Austin
	Christiansen, Harold A.	Jackson
†	Chulman, Miguel A.	Rochester
†	Chumbley, Lee C.	Rochester
	Chunn, Stanley S.	Willmar
	Church, Gerald E.	Two Harbors
	Cich, John A.	West St. Paul
	Ciriacy, Edward W.	Ely
	Clagett, O. Theron	Rochester
	Clapp, Hubert D.	Crookston
	Clark, Elizabeth A. (Mrs. Halbert)	Duluth
†	Clark, Harry B.	St. Cloud
	Clark, Ivan T.	Duluth
†	Clark, Leslie W.	Manchester, IA
	Clark, Malcolm D.	Minneapolis
	Clark, Robert S.	Minneapolis
	Clark, W. Bruce	St. Paul
†	Clarke, Dean T.	Faribault
	Clarke, John W.	Waconia
	Clay, Lyman B.	Minneapolis
*	Cleaves, William D.	Sauk Centre
	Clifford, George W.	Alexandria
†	Clifton, Theodore A.	Hollywood, FL
	Cline, David W.	Minneapolis
	Closuit, Frederick C.	Aitkin
	Cochrane, Byron B.	St. Paul
	Cochrane, Ray F.	Minneapolis
	Coddon, Walter D.	St. Paul
	Code, Charles F.	Rochester
#	Coder, Donald M.	FPO, NY
	Cody, D. Thane	Rochester
	Coe, John I.	Minneapolis
	Cohan, Richard C.	Minneapolis
	Cohen, Bernard A.	Minneapolis
	Cohen, Ephraim B.	Minneapolis
	Cohen, Henry W.	Wayzata
†	Cohen, Manley	Rochester
	Cohen, Sumner S.	Minneapolis
	Colago, Victor M.	Browns Valley
	Colby, Malcolm Y., Jr.	Rochester
†	Colby, Woodard L.	St. Paul
	Cole, George A.	Albert Lea
	Cole, James S.	Minneapolis
	Cole, Wallace H.	St. Paul
	Coleman, John B.	St. Paul
†	Coleman, Robert L.	Rochester
	Coleman, Thomas P.	Minneapolis
	Coles, Douglas T.	Rochester
	Coll, James J.	Duluth
†	Collins, Arthur N.	Duluth
†	Collins, Roger T.	Rochester
†	Collison, Robert W.	Rochester
	Colliton, Patrick A.	Moorhead
	Colman, Edward L.	Fergus Falls
	Colton, Roger S.	St. Paul
	Comfort, Thomas H.	St. Paul
	Conley, Francis W.	Duluth
	Conley, Robert H.	Mankato
	Conlin, F. Dixon	Minneapolis
	Conlon, Daniel C.	Minneapolis
†	Conn, Doyt L.	Rochester
†	Conn, Richard L.	Rochester
	Connolly, Coleman J.	St. Paul
	Connolly, Daniel C.	Rochester
	Connolly, Joseph P.	West St. Paul
†	Connor, Charles E.	St. Paul
†	Connor, David G.	Minneapolis
†	Cook, C. Kenneth	St. Paul
	Cook, Edward N.	Rochester
	Coombs, Carl H.	Cass Lake
	Cooper, Charles C.	Moose Lake
#	Cooper, Herbert A.	Wheatland, CA
	Cooper, John P.	Minneapolis
	Cooper, Robert R.	Minneapolis
	Cooper, Talbert	Rochester
†	Cooperman, Avram M.	Rochester
	Cope, Hershel B.	Virginia
	Corbin, Kendall B.	Rochester
#	Corcoran, James R.	Orange Park, FL
†	Corniea. Albert D.	Minneapolis
	Correa, Dale H.	Minneapolis
	Corrigan, Cyril J.	Rochester
	Corson, Wilfred A.	Minneapolis
	Cortez, Daniel P.	Minneapolis
	Cosgriff, James A., Jr.	Olivia
†	Cotton, Gerald E.	Rochester
	Cottor, Robert E.	Duluth
	Coulter, Harold E.	Minneapolis
†	Countryman, Roger S.	Saratoga, CA
	Coventry, Markham B.	Rochester
	Coventry, William D.	Duluth
	Covey, Kenneth W.	Moorhead
	Cowan, Donald W.	Minneapolis
	Cowan, Gary A.	Duluth
	Cowan, George M.	Duluth
	Cowger, Robert C.	Farmington
	Cox, Russell L.	Estherville, IA
	Coy, Douglas J.	Grand Rapids
	Craig, David M.	St. Paul
	Craig, M. Elizabeth	Minneapolis
	Cram, Barclay M.	St. Paul
	Cramer, Glen G.	New Brighton
†	Cranmer, Richard R.	Laguna Hills, CA
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†	Creasman, John P.	Rochester
	Creevy, Charles D.	Minneapolis
	Creps, James R.	Duluth
	Cronwell, Bernhard J.	Austin
	Crow, Earl R.	Minnetonka
	Crow, George M.	International Falls
#	Crowder, Bennett L., II	Ft. Campbell, KY
	Crowley, James H.	St. Paul
	Crowley, Leonard V.	Minneapolis
	Crudo, Vincent D.	St. Paul
	Crum, Arthur Z.	St. Paul
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†	Crutchfield, Susan E.	Fairchild AFB, WA

	Cullado, Andrionico F.	Minneapolis
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	Culligan, Leo C.	Minneapolis
	Culp, Clyde E.	Rochester
	Culp, Ormond S.	Rochester
	Culver, Lucian G.	St. Paul
	Cumming, Edward D.	St. Paul
	Cumming, Robert J.	St. Cloud
	Cundy, Donald T.	Minneapolis
	Cupps, Roger E.	Rochester
	Curran, John P.	Anoka
	Cushing, Richard T.	Minneapolis
†	Cutts, George	Minneapolis

D

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	Daggett, Donald R.	Minneapolis
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	Dahl, James C.	Minneapolis
†	Dahl, John A.	Minneapolis
	Dahlin, David C.	Rochester
	Dahlquist, LaRue V.	Pipestone
	Dale, Allan J. D.	Rochester
	Dale, Les N.	Hastings
	Daly, Alfred E.	St. Paul
	Damberg, Sheldon W.	St. Paul
†	Daniel, Donald H.	Minneapolis
†	Daniel, William W.	Rochester
	Danielson, Lennox	Litchfield
†	Dankmyer, Frederick L.	Rochester
	Danyluk, Michael	Minneapolis
	Dargay, Cyril P.	Minneapolis
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	Daugherty, Guy W.	Rochester
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†	David, Ronald B.	Rochester
†	Davidson, Allan D.	Rochester
	Davignon, Jean	Montreal, Quebec
†	Davis, Austin C.	Pompano Beach, FL
	Davis, Edward V.	St. Paul
	Davis, Eunice A.	St. Paul
	Davis, George D.	Rochester
*†	Davis, Jay C.	Pompano Beach, FL
†	Davis, Lloyd T.	Wadena
	Davis, Luther F.	Wadena
#	Davis, Michael W.	APO, NY
	Davis, Raymond D.	Stockton, CA
	Davis, Thomas H.	Minneapolis
	Davis, William I.	Moose Lake
	Dawson, James R.	St. Paul
	Dawson, Lorin D.	Worthington
	Dawson, Walter J., Jr.	Minneapolis
	Dearing, William H.	Rochester
	Deason, Keith B.	Chisago City
	Decker, Charles H.	St. Paul
	Decker, David G.	Rochester
†	Dedeker, Kenneth L.	Minneapolis
	Degallier, Daniel	Winona
†	Deger, Grant E.	Rochester
	Delahunty, John R.	Red Wing
	deLeon, Buenaventura	Stillwater
	Delmore, John L.	Roseau
	Delzell, Allen W.	Minneapolis
	De Marais, Lloyd C.	Hibbing
†	De Marco, Peter R.	Rochester
	Demo, Robert A.	Albert Lea
	Derauf, Donald E.	St. Paul
	Derechin, William	St. Paul
	DeRemee, Richard A.	Rochester
	Desai, B. J.	Worthington
†	Detenbeck, Lee C.	Rochester
	Deters, Donald C.	St. Paul
	Deutsch, Robert J.	Duluth
	Devine, Kenneth D.	Rochester
	Devloo, Robert A.	Rochester
	De Weerd, James H.	Rochester
	De Weerd, Robert W.	Owatonna
	Deweese, Wilford J.	Bemidji
	Dewey, Donald H.	Owatonna
	Diamond, Robert A.	Minneapolis
	Dickman, Roy W.	Minneapolis
	Dickson, Franklin H.	Proctor
	Didier, Edward P.	Rochester
	Diefenbach, Eugene J.	Minneapolis
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	Diehl, James J.	Minneapolis
	Dierker, Heinrich A.	Minneapolis
†	Diessner, Ardell W.	Redwood Falls
	Diessner, Grant R.	Rochester
†	Diessner, Henry D.	Minneapolis
	Dietrich, Donald E.	St. Paul
	Dillie, Donald E.	Litchfield
	Dillenburg, Cyril J.	Crookston
	Dinapoli, Robert P.	Rochester
	Dines, David E.	Rochester
†	DiPasquale, Joseph A.	Rochester
	Disney, Thomas F.	Rochester
†	Dittrich, Raymond	St. Paul
	Divertie, Matthew B.	Rochester
*†	Dixon, Claude F.	Rochester
†	Dixon, George D.	Rochester
	Doan, Robert E.	Wayzata
	Dobbs, Richard L.	Duluth
	Dobler, Manfred G.	Ely
	Dobson, Mervin W.	Mankato
	Dobyns, James H.	Rochester
	Docherty, John A.	Edina
	Dockerty, Malcolm B.	Rochester
	Docksey, John W.	Willmar
	Dodds, William C.	Detroit Lakes
	Dodson, Albertus F.	Brainerd
	Doebler, Myron I.	Mora
	Doherty, Elmer M.	New Prague
	Dokken, James H.	Windom
	Dolmage, George H.	St. Paul
	Doman, Victor W.	Lakefield

Doms, Vernon A.	Elbow Lake
Donaldson, Charles S.	St. Cloud
Donatelle, Edward P.	Minneapolis
Donoghue, Francis E.	Rochester
Donovan, Daniel L.	New Brighton
Dooley, Robert T.	St. Paul
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Dornbach, Robert A.	Minneapolis
Dorsey, George C., Jr.	Minneapolis
Dorsey, William E.	Minneapolis
Doscherholmen, Alfred	Minneapolis
Dougan, Jerome W.	Minneapolis
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Douglass, Bruce E.	Rochester
Douglass, Jesse E.	Cannon Falls
do Vale, Joao M.	Minneapolis
† Doxey, Gilbert L.	Minneapolis
Doyle, James R.	Rochester
† Dozois, Roger R.	Rochester
Dredge, Thomas E.	Minneapolis
† Dredge, Thomas E., Jr.	Minneapolis
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Drexler, George W.	Blue Earth
Dreyling, Roger A.	Eden Valley
Drill, Frederick E.	Minneapolis
Drill, Herman E.	Hopkins
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† Dry, Thomas J.	Rochester
† Dubois, David D.	Rochester
Dubois, Julian F.	Sauk Centre
Duff, Edwin R.	Minneapolis
Duffy, John C.	Minneapolis
Dummer, Donald J.	New Brighton
Dumoneaux, Roland G.	Minneapolis
Duncan, Donald A.	Minneapolis
Duncan, James W.	Moorhead
Dunlap, David J.	Minneapolis
Dunlap, Earl H.	Minneapolis
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Dunn, Robert C.	St. Paul
† Dunn, Robert J.	Rochester
Dunstan, Paul L.	Willmar
Dupont, Joseph A.	Excelsior
Durkin, John L.	St. Paul
Duryea, Marbry	Minneapolis
Duryea, Willis M.	Minneapolis
Duryea, Willis M., Jr.	Minneapolis
Duthoy, Everette J.	St. Paul
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Duvall, Arndt J., III	St. Paul
Duvoisin, George E	Rochester
Dvorak, Benjamin A.	Minneapolis
Dwan, Paul F.	Minneapolis
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Dwyer, John J.	Duluth
Dyck, Peter J.	Rochester
Dyer, John Allen	Rochester
Dyrdal, Paul J.	St. Paul
Dysterheft, Adolf F.	Gaylord

E

Earl, George A.	St. Paul
Earl, John R.	St. Paul
Earl, Stephan H.	Minneapolis
Eaton, David B.	Worthington
Eberley, Tobe S.	Benson
Ebert, Richard V.	Minneapolis
Eckdale, John E.	Mankato
# Eckelberg, Merlyn E.	APO, NY
Eckerly, Jean R.	Minneapolis
Eckert, Joseph F.	Mankato
Eckman, Philip F.	Duluth
Eckman, Philip L.	Duluth
Eckman, Ralph J.	Duluth
Eder, Walter P.	Minneapolis
Edmondson, Hugh A., Jr.	Minneapolis
Edwards, J. Willard	St. Paul
Edwards, Jesse E.	St. Paul
Edwards, Lloyd G.	St. Paul
Edwards, Richard B.	St Paul
Edwards, Thomas J.	St. Paul
# Edwards, Walter G., Jr.	Bethesda, MD
Edwin, Russell L.	North Mankato
Eelkema, Herman H.	St. Paul
Efteland, Myles E.	Minneapolis
Egge, Sanford G.	Albert Lea
Eginton, Charles T.	Fargo, ND
† Ehrenberg, Claude J.	Minneapolis
Ehrlich, S. Paul	Minneapolis
Eich, Matthew A.	Minneapolis
Eichelberger, Dale L.	Willmar
Eichenlaub, John E	Minneapolis
Eichhorn, Edmund P., Jr.	Minneapolis
Eide, O. A.	Hancock
† Eiden, Vera M.	Afton
Eilers, Vincent E.	St. Paul
Eilers, William B.	Redwood Falls
Eisenbeis, C. F.	Mankato
Eisenman, Walter	Hibbing
† Eisenstadt, David H.	Minneapolis
Eisenstadt, William S.	Minneapolis
Eitel, George D.	Minneapolis
† Ekdale, Robert A.	Menlo Park, CA
Eklund, Carl D.	Duluth
Elkins, Earl C.	Rochester
Ellertson, Leonard M.	Albert Lea
Ellinger, Albert J.	Willmar
Ellingson, Richard B.	Minneapolis
Ellington, Anna L.	Minneapolis
Elliott, Harold J.	Hayfield
Elliott, J. W.	Mankato
Ellis, Earl W.	Elgin
Ellis, F. Henry, Jr.	Rochester
Ellis, Ronald W.	St. Paul
Ellison, Evan S.	Minneapolis
† Ellison, Frank E.	Monticello
Ellwood, Paul M., Jr.	Minneapolis
† El Shahawy, Mahfouz A.	Rochester
Emanuel, Karl W.	Duluth

	Emerson, Edward C.	St. Paul
	Emerson, Edwin E.	Osakis
†	Emerson, Robert K.	Rochester
†	Emmett, John L.	Rochester
	Emmons, Robert W.	St. Paul
†	Emmons, William F.	Rochester
*†	Emond, Albert J.	Farmington
	Emond, Joseph S.	Farmington
	Emond, Joseph S., Jr.	Minneapolis
	Endress, Edward K.	St. Paul
†	Engberg, Edward J.	Faribault
	Engebretson, Paul	Alexandria
	Engel, Andrew G.	Rochester
	Engel, Joseph P.	Minneapolis
†	Engelberg, Jerry	Rochester
	Engelsgjerd, Gerald L.	Duluth
	Engelstad, Wendell P.	Eveleth
	England, Rodney W.	St. Paul
	Englund, Elvin F.	Minneapolis
†	Engstrand, Oscar J.	Minneapolis
	Engstrom, E. Duane	Minneapolis
	Engstrom, George	St. Peter
	Engstrom, Robert B.	Mankato
	Engwall, Richard L.	Minnetonka
	Enroth, Oscar E.	St. Paul
	Erdal, Ove A.	Columbia, MO
	Erich, John B.	Rochester
	Erickson, Alvin O.	Long Prairie
	Erickson, Clifford O.	Minneapolis
	Erickson, Donald J.	Rochester
	Erickson, Laurence F.	Minneapolis
	Erickson, Myron E.	Minneapolis
	Erickson, Reuben F.	Minneapolis
	Erickson, Robert L.	Rosemount
	Erickson, Vernon D.	Grand Rapids
	Erling, Carl B.	St. Paul
	Erlanson, A. Cornell	St. Paul
†	Errico, James M.	Rochester
†	Ersek, Robert A.	Minneapolis
	Ersfeld, Murray P.	St. Paul
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	Esensten, Sidney	Minneapolis
	Espelien, Alan D.	St. Cloud
	Espinosa, Raul E.	Rochester
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	Estrem, Robert D.	Fergus Falls
†	Ettinger, David S.	Rochester
	Ettinger, Milton G.	Minneapolis
	Etzwiler, Donnell D.	Minneapolis
	Eustermann, John J.	Mankato
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	Evans, Leslie M.	Sauk Rapids
†	Evans, Titus C., Jr.	Rochester
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	Evensta, John B.	Grand Rapids
	Everhart, Clarence E., Jr.	Minneapolis
	Evison, Emerson O.	Duluth
	Ewens, George B.	Virginia
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F

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	Farrell, T. Edwin	Minneapolis
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	Feigal, Gary R.	Lake City
	Feigal, William M.	Fairmont
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	Feinberg, Philip	Minneapolis
	Feinberg, Samuel B.	Minneapolis
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	Ferguson, John N.	St. Paul
	Ferguson, Richard H.	Rochester
	Fernandez, Rafael F., Jr.	Minneapolis
	Ferrell, Clarence R.	Grand Rapids
	Ferris, Deward O.	Rochester
	Fesenmaier, Otto B.	Los Angeles, CA
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	Fetzek, Albert D.	Minneapolis
	Feuling, John C.	Duluth
	Field, Charles A.	Rochester
	Field, Charles W.	Hopkins
	Fifer, Ellen Z.	St. Paul
	Fifer, William R.	Minneapolis
	Fifield, Malcolm M.	Duluth
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	Filipovich, Orest N.	Minneapolis
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†	Finch, John E.	Rochester
	Fingerman, David L.	Minneapolis
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	Fink, Leo W.	Minneapolis
	Fink, Robert J.	Minneapolis
†	Fink, Walter H.	Minneapolis

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	Fischer, Albert P.	Wayzata
	Fischer, Robert F.	St. Paul
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	Fisher, Dan W.	St. Paul
†	Fisher, Darrell E.	Rochester
	Fisher, Don H.	Minneapolis
	Fisher, Isadore I.	Minneapolis
	Fisketti, Henry	Duluth
	Fitch, Charles G.	Worthington
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	Fitzsimons, William E.	Brainerd
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†	Flanigan, Donald J.	Rochester
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	Fliehr, Richard R.	Minneapolis
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	Floersch, Adrian J.	Owatonna
	Flom, Reynold P.	St. Paul
	Flom, Robert S.	St. Paul
	Flora, George C.	Minneapolis
	Florence, David W.	Robbinsdale
	Florine, Martin C.	Mankato
	Flory, William D.	Minneapolis
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	Flynn, Bernard F.	Hibbing
	Flynn, Louis L., Jr.	St. Paul
	Flynn, Robert A.	St. Paul
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†	Fogarty, Charles W.	St Paul
	Fogelberg, Emil J.	St. Paul
	Foker, Leslie W.	Minneapolis
	Foley, Robert R.	Minneapolis
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	Foley, William A.	Minneapolis
	Folsom, Louis B.	Minneapolis
	Fontana, Robert S.	Rochester
	Forbes, Edward F.	Minneapolis
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	Ford, W. Harold	Hopkins
	Foreman, Richard T.	St. Paul
†	Forker, Alan D.	Rochester
	Forsythe, James R.	St. Paul
	Fortier, George M. A	Little Falls
	Fortier, Rene G.	Mankato
†	Foss, Edward L.	Condon, MT
†	Foster, David A.	Rochester
	Foster, Orley W.	Minneapolis
#	Foster, Thomas N., III	Whidbey Island, WA
	Foulk, William T., Jr.	Rochester
†	Fowler, Franklin, Jr.	Rochester
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	Fox, LeRoy J.	St. Paul
†	Fraker, Keith E.	Rochester
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	Francis, David W.	Morristown
	Frane, Donald B.	Minneapolis
	Frane, Gerald T.	Minneapolis
	Franklin, Gordon W.	Northome
	Fredericks, George M.	Minneapolis
†	Frederickson, Alice C.	Willmar
	Fredlund, Jon S.	Minneapolis
†	Freedman, Harvey M.	Rochester
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	Freeman, Charles D., Jr.	St. Paul
	Freeman, Craig W.	Minneapolis
	Freeman, Donald W.	St. Louis Park
	French, Bayard T.	Hibbing
	French, Lyle A.	Minneapolis
	Frethem, Allen A.	Rochester
	Frey, Richard J.	Minneapolis
	Friberg, Joseph B.	Minneapolis
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	Fried, Louis A.	Minneapolis
†	Friedell, Aaron	Minneapolis
	Friedell, George	Minneapolis
	Friedlieb, Oskar P.	Virginia
	Friedman, Harry S.	Minneapolis
	Friedrich, Bradford E.	Red Wing
	Friend, Charles A.	Minneapolis
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	Fritsche, Carl J.	New Ulm
	Fritsche, Theodore R.	New Ulm
	Fritz, Wallace L.	St. Paul
	Froats, Charles W.	St. Paul
	Frost, John B.	Minneapolis
	Fruchtman, Stanley A.	Minneapolis
	Frye, Charles W.	St. Paul
	Frykman, Howard M.	Minneapolis
	Frys, Russell N.	Minneapolis
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	Fuglestad, J. Roald	Minneapolis
	Fulks, Raymond W.	Minneapolis
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	Fuller, Benjamin F.	White Bear Lake
†	Fuller, Edwin B.	Rochester
	Fuller, Josiah	Duluth
†	Fulton, Richard E.	Rochester
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	Funke, Joyce L.	St. Paul
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	Furman, L. Christine	Minneapolis
†	Furman, Philip John	Rochester
	Furr, Leo	Bird Island
†	Furszyfer, Jacob	Rochester
	Fusaro, Ramon M.	Minneapolis

G

Gaard, Richard C.	Robbinsdale
Gaebe, Milton B.	Clara City
Gaertner, Frank M. J., Jr.	St. Paul
Gaertner, John R.	St. Paul

	Gaida, Joseph B.	St. Cloud
	Gailitis, Veronika M.	St. Paul
	Galbraith, Richard F.	Minneapolis
	Galejs, Aina	Minneapolis
	Gallett, Lester E.	Minneapolis
	Galligan, John J.	St. Paul
†	Galligan, Margaret Mary D.	Minneapolis
	Galloway, Jackson R.	Alexandria, LA
	Galway, Charles F.	Minneapolis
†	Gambill, Carl M.	Rochester
	Gambill, Earl E.	Rochester
	Gamble, Elbert J.	Roseville
	Gamble, William G.	Minneapolis
	Gamm, Edgar R.	Park Rapids
	Garamella, Joseph J.	Minneapolis
	Gannon, Paul G.	Minneapolis
	Garber, George L.	Winona
	Garber, James J.	Rochester
	Gardner, Jack K.	Fairmont
†	Gardner, Victor H.	Fairmont
	Gardner, Walter P.	St. Paul
	Garetz, Floyd K.	Minneapolis
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	Garrow, Douglas M.	St. Paul
	Garske, George L.	Minneapolis
	Garten, Joseph L.	Minneapolis
	Garvey, James T.	Minneapolis
	Gasik, Joseph M.	Minneapolis
#	Gasior, Robert M.	Houston, TX
	Gastineau, Clifford F.	Rochester
†	Gau, Gerald T.	London, England
	Gault, Neal L., Jr.	APO San Francisco, CA
	Gaute, Svend T.	St. Paul
	Gaviser, David	Minneapolis
	Gedge, Stafford W.	Rochester
†	Gehlen, Joseph N.	St. Paul
	Geib, Marvin J.	Fargo, ND
	Geiser, Peter M.	Alexandria
	Geist, Robert W.	St. Paul
	Geller, Joseph	Minneapolis
	Gendron, Joseph L.	St. Paul
†	Gentling, Peter A.	Rochester
	George, Vane P., Jr.	LeSueur
	Geraci, Joseph E.	Rochester
	Gerend, Thomas J.	Virginia
	Gerstenkorn, George B.	Milaca
	Gerster, Paul W.	Anoka
†	Gesundheit, Sim	Rochester
	Geurs, Benjamin R.	Mankato
†	Ghostley, Mary C.	Minneapolis
	Gibbs, Edward C.	St. Paul
	Gibbs, Robert W.	Minneapolis
	Giebenhain, John N.	Minneapolis
	Giere, Joseph C.	Minneapolis
	Giere, Richard W.	Minneapolis
†	Giere, Silas W.	Benson
*†	Griffin, Herbert Z.	Rochester
#	Gilbaugh, James H., Jr.	Eglin, FL
	Gilbert, Maurice G.	Minneapolis
	Gilbertsen, A. Sigrid	Minneapolis
	Gilbertsen, Victor A.	Minneapolis
	Gilchrist, Milton R.	St. Paul
†	Gildersleeve, John W.	Rochester
	Gildersleeve, Robert G.	Watertown
	Gill, Theodore M.	Albert Lea
#	Gilles, Paul J.	Great Lakes, IL
	Gilles, Thomas F.	Fairfax
	Gillespie, Delmar R.	St. Paul
	Gillespie, Malcolm G.	Duluth
†	Gilman, Lloyd C.	St. Paul
	Gilsdorf, Donald A.	St. Paul
	Gingold, Benjamin A.	Minneapolis
	Gislason, Paul H.	Mankato
#	Gisvold, John J.	APO San Francisco, CA
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	Gjerde, William P.	Lake City
	Glaeser, John H.	Minneapolis
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	Glenny, William R.	St. Paul
	Glick, Dallas D.	Mountain Lake
	Glomstad, Gary B.	Deer River
†	Gobel, Fredarick L.	Minneapolis
	Goblirsch, Andrew P.	Sleepy Eye
	Godfrey, H. Wilson	Minneapolis
	Goehl, Reinhold O.	Minneapolis
	Goehrs, Gilman H.	St. Cloud
†	Goellner, John R.	Rochester
	Gokcen, Barbara W.	Minneapolis
	Gokcen, Muharrem	Minneapolis
	Gold, David	Minneapolis
	Goldberg, Isadore M.	Minneapolis
	Goldberg, Marvin E.	Minneapolis
	Goldberg, Robert J.	St. Paul
	Goldberg, Stanley M.	Minneapolis
	Goldfarb, Benjie L.	Minneapolis
	Goldfarb, Mace G.	Minneapolis
	Goldish, Daniel R.	Duluth
	Goldish, Robert J.	Duluth
†	Goldman, Sherwin	Rochester
†	Goldman, Theodore I.	Minneapolis
†	Goldner, John C.	Rochester
	Goldner, Meyer Z.	Minneapolis
	Goldschmidt, Volker	Duluth
	Goldsmith, Joseph W.	St. Paul
	Goldstein, Alan L.	Hopkins
	Goldstein, Norman P.	Rochester
	Goldston, Edgar C.	Rochester
	Gomez, Manuel R.	Rochester
	Good, C. Allen, Jr.	Rochester
	Good, Gary	Minneapolis
	Good, Roy H.	Northfield
	Goodchild, William R.	Minneapolis
	Goodman, Ernest	St. Paul
	Goodnow, William H.	Duluth
†	Goodwin, Henry N.	Rochester
	Goott, Bernard	St. Paul
	Gordon, John R.	Minneapolis
	Gordon, Sewell S.	Minneapolis
#	Goren, Hershel	APO, San Francisco, CA
	Gorman, Columba A.	Rochester
	Gould, Allan B., Jr.	Rochester
†	Gould, Ronauld J.	Rochester
	Govrik, Kalman	St. Paul
	Gowan, Lawrence R.	Duluth
	Gowan, Lawrence R., Jr.	Duluth
	Gozum, Ekrem	Minneapolis
†	Gracey, Douglas R.	Rochester
†	Graf, John A.	Rochester
	Graham, Asa B.	Faribault
	Graham, John J.	Minneapolis
	Grahek, Jack P.	Ely
	Grande, David W.	Mankato
	Granquist, Richard D.	Minneapolis
	Grant, John C.	Sauk Centre
	Grant, Suzanne	Minneapolis
†	Gratzek, Frank R.	Anoka
	Gravett, Desmond C.	Rochester
†	Gray, Royal C.	Minneapolis

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	Green, Clayton R.	Excelsior
	Green, Paul A.	Rochester
	Green, Robert A.	St. Louis Park
	Greenberg, Albert J.	Minneapolis
†	Greenberg, Burton H.	Rochester
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	Greene, Jerry G.	St. Paul
	Greene, Laurence F.	Rochester
	Greene, Leonard H.	Minneapolis
	Greenfield, Irving	Minneapolis
	Greenfield, William T.	Dallas, TX
	Greenwald, Stephen M.	Minneapolis
	Gregg, James A.	Rochester
	Gregoire, Earl	Bemidji
¶	Greisheimer, Esther M.	Philadelphia, PA
	Gretsch, Gerald A.	St. Paul
	Gridley, John W.	Minneapolis
	Griebie, Grant L.	Hutchinson
	Griffin, John W.	Bemidji
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	Griffin, Richard P.	Benson
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†	Griffiths, Robert W.	Rochester
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	Grimes, Marian	Minneapolis
	Grimes, Paul T.	Park Rapids
	Grimmell, Francis J.	Minneapolis
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	Grinvalds, Anna O.	Cambridge
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†	Groschupf, Theophilus P.	Bemidji
	Grose, Frederick N.	Clarissa
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	Gudio, Felix A., Jr.	St. Paul
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	Guilfoile, Pierre J.	Delano
	Gullickson, Glenn, Jr.	Minneapolis
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	Gustason, Harold T.	Minneapolis
	Gustilo, Ramon B.	Minneapolis
	Guthrie, J. Cameron	St. Paul
	Guy, Jack A.	New London

H

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	Hagen, Kristofer	Minneapolis
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	Hakanson, Erick Y.	St. Paul
	Hakim, Ali A.	Minneapolis
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	Halenbeck, Philip L.	St. Cloud
	Hall, Arthur M.	Minneapolis
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	Hall, Harry B.	Minneapolis
	Hall, Jack W.	Rochester
	Hall, Wendell H.	Minneapolis
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	Hansen, Robert E.	Hibbing
	Hansen, Rollin M.	Minneapolis
	Hansen, Theodore M.	Albert Lea
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	Hanson, Everett C.	New York Mills
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	Hanson, Harold W.	Minneapolis
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	Hanson, Lewis	Frost
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†	Harrington, Stuart W.	Rochester
	Harrington, Vernon A.	Duluth
	Harris, John E.	Minneapolis
	Harris, Leon D.	Minneapolis
	Harris, Lloyd E.	Rochester
	Harris, Max E.	St. Paul
	Harrison, Edgar G., Jr	Rochester
	Harrison, Percy W.	Worthington
	Harrison, William C.	Minneapolis
	Hart, William E.	Monticello
	Hartfiel, William F.	St. Paul
#	Hartfield, James E., Jr.	Columbia, SC
	Hartig, Marjorie	St. Paul
	Hartig, Paul R.	Minneapolis
	Hartjen, Jason K.	Bemidji
	Hartman, Evelyn E.	Minneapolis
	Hartnagel, Grant F.	Red Wing
	Hartridge, Virginia B.	Rochester
	Hartung, Elmer H.	Claremont
	Hartwich, Roger F.	Winona
	Hartwig, John A.	Minneapolis
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	Hass, Frederick M.	Minneapolis
	Hastings, Donald W.	Minneapolis
†	Hastings, John D.	Rochester
†	Hatayama, Yoshiyuki	Rochester
#	Hathaway, David S.	Arlington, VA
	Haugan, Norman R.	Park Rapids
	Hauge, Erling T.	Minneapolis
†	Hauge, Malvin I.	Marcell
	Haugen, George W.	Minneapolis
	Haugen, John A.	Minneapolis
	Hauser, Charles W.	St. Paul
	Hauser, Donald C.	Minneapolis
*†	Hauser, George W.	Seattle, WA
†	Hauser, Victor P.	St. Paul
†	Hauser, W. Allan	Rochester
	Havel, Robert J.	Minneapolis
	Haven, Walter K.	Minneapolis
†	Havig, Terrance A.	Rochester
	Hawk, Dale J.	St. Charles
	Hawkinson, Harlan W.	St. Paul
†	Hawkinson, Raymond P.	Minneapolis
	Hawley, George M. B., II	Red Wing
	Hay, Lyle J.	Minneapolis
†	Hayashi, Melvin M. K. W.	Rochester
	Hayes, Albert F.	St. Paul
	Hayles, Alvin B.	Rochester
	Hays, Albert T.	Minneapolis
#	Hays, James C.	APO New York, NY
	Haywa, E. William	Minneapolis
	Hazen, Richard W.	Willmar
	Head, Douglas P.	Minneapolis
	Hebbel, Robert	Minneapolis
†	Hebeisen, Milton B.	Chaska
†	Heck, Frank J.	Rochester
†	Heck, William W.	St. Paul
	Hedemark, Homer H.	Ortonville
	Hedemark, Truman A.	Ortonville
	Hedenstrom, Charles W.	St. Paul
†	Hedenstrom, Frank G.	St. Paul
	Hedenstrom, Paul H.	Princeton
	Hedenstrom, Philip C.	Marshall
	Hedenstrom, Richard H.	St. Paul
	Hedlund, Charles J.	St. Paul
	Hedrick, William L.	Minneapolis
	Heegaard, William G.	Alexandria
	Hegrenes, Robert L.	Hutchinson
	Hegstad, Thomas C.	Windom
	Heiam, William C.	Cook
	Heiberg, Olaf M.	Worthington
	Heid, James K.	Little Falls
†	Heidel, Werner	Cresskill, NJ
	Heilig, William R.	St. Paul
	Heimark, John J.	Mankato
	Heinz, Ivy B.	Shakopee
	Heinz, John N.	Minneapolis
	Heinzerling, Carl R.	Chaska
	Heise, Carl vR.	Winona
	Heise, Herbert vR.	Winona
	Heise, Paul vR.	Winona
	Heise, Philip vR.	Winona
	Heise, William vR.	Winona
	Heisel, John G.	Duluth
	Held, William J.	St. Cloud
	Heller, Edgar E.	Mankato
	Helmholz, Henry F., Jr.	Rochester
	Helseth, Hovald K.	Fergus Falls
	Helwig, Karl L.	Virginia
#	Henderson, Darrell L.	Portsmouth, VA
	Henderson, Edward D.	Rochester
	Henderson, John W.	Rochester
	Henderson, Lowell L.	Rochester
	Henderson, Terrance P.	White Bear Lake
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	Henke, Wilbert J.	St. Paul
	Henrikson, Earl C.	Minneapolis
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	Henry, Harold W.	Moose Lake
	Henry, James S.	St. Paul
	Henry, John C.	Owatonna
	Henry, Joseph E.	Milaca
	Henry, Kenneth G.	Owatonna
	Hepper, Norman G.	Rochester
	Herber, Leo	Thief River Falls
	Herbert, Willis L.	Minneapolis

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	Herman, Samuel M.	St. Paul
	Hermans, Paul E.	Rochester
	Herrick, Donald W.	St. Paul
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	Hess, Carroll N.	Minneapolis
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	Hewitt, Marshall I.	Minneapolis
†	Hewitt, Richard M.	Clearwater Beach, FL
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	Hickok, David F.	Minneapolis
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	Higgins, John A.	Rochester
	Hildebrand, John E.	Bemidji
	Hildebrandt, Walter C.	Minneapolis
	Hilding, Anderson C.	Duluth
	Hilgedick, William R.	St. Paul
	Hilger, Jerome A.	St. Paul
	Hilger, John R.	St. Paul
	Hilger, Laurence D.	St. Paul
	Hilgermann, George O.	Minneapolis
	Hilker, Marcus D.	St. Paul
	Hilker, Robert T.	Owatonna
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	Hill, Earl	Minneapolis
	Hill, Elmer M.	Minneapolis
	Hill, John R.	Rochester
	Hill, Richard W.	Rochester
	Hiller, Bruce H.	Minneapolis
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	Hinderaker, Harris P.	Willmar
	Hines, Edgar A., Jr.	Brevard, NC
†	Hiniker, Louis P.	St. Paul
	Hiniker, Peter J.	St. Peter
	Hinz, Walter E.	Willmar
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	Hirsh, Stanton A.	Crookston
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	Hodges, Kenneth V.	Minneapolis
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	Hodgson, Jane E.	St. Paul
	Hodgson, John R.	Rochester
	Hoeg, Dwight C.	Duluth
†	Hoehn, James G.	Rochester
	Hoeper, Philip G.	Mankato
	Hoff, Herbert O.	Duluth
	Hoffert, Henry E.	Minneapolis
	Hoffman, David L.	Rochester
	Hoffman, Roy A.	Minneapolis
	Hoffman, Walter Lees	Minneapolis
	Hofmann, Gerald N.	Minneapolis
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	Holbrook, Margaret A.	Rochester
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†	Holcomb, O. William	St. Paul
	Holland, C. R.	Rochester
	Hollenhorst, Robert W.	Rochester
	Holley, Keith E.	Rochester
	Hollinshead, W. H.	St. Paul
	Holm, Donald F.	Minneapolis
	Holm, Owen W.	Crookston
	Holman, Colin B.	Rochester
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	Holt, Glen E.	Duluth
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	Holten, David R.	Minneapolis
	Holten, John	Moorhead
	Holzapfel, Fred C.	Minneapolis
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	Honath, Donald H.	Owatonna
	Hood, Roderick P.	Duluth
	Hoover, Norman W.	Rochester
	Hopkins, G. Wendell	Minneapolis
	Hopperstad, J. Jerome	Minneapolis
	Hoppes, Emerson E.	Minneapolis
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	Horns, Richard C.	Minneapolis
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	Hoseth, Wayne L.	Minneapolis
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	Hottinger, Raymond C.	Janesville
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	Houkom, S. Sverre	Duluth
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	Hovde, Gordon W.	Lindstrom
	Hovland, Melvin L.	Minneapolis
	Hovland, Richard D.	Minneapolis
	Howard, Frank M., Jr.	Rochester
	Howard, Robert B.	Minneapolis
	Howard, Solomon E.	Minneapolis
	Howe, Newell W.	West St. Paul
	Howell, Carter W.	Minneapolis
	Howell, John L.	Minneapolis
	Howell, Llewelyn P.	Rochester
	Hoyer, Ludolf J.	Oshkosh, WI
	Hoyt, C. Sherman	Minneapolis
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	Huber, Robert W.	St. Croix Falls, WI
	Hubin, Edwin G.	Sandstone
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	Hunt, Vincent R.	Red Lake Falls
	Hunter, Murray H.	Farmington
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†	Hynes, Kieran M.	Rochester

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	Jacobson, Ferdinand C.	Duluth
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	Jastram, Rupert M.	St. Paul
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	Jensen, Nathan K.	Minneapolis
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	Jerome, Elizabeth B. K.	Minneapolis
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	Jessico, Charles M.	Duluth
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†	Johanson, Waldemar G., Jr.	Dallas, TX
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	Johnson, Alan R.	Windom
	Johnson, Angelo G.	Minneapolis
	Johnson, Arthur B.	Minneapolis
	Johnson, Bradley D.	Minneapolis
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	Johnson, Carl Eric	Rochester
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	Johnson, C. Percy	Tyler
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	Johnson, Curtis M.	Winona
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	Johnson, David R.	Minneapolis
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	Johnson, Edward A.	Minneapolis
†	Johnson, Einer W.	Bemidji
	Johnson, Einer W., Jr.	Rochester
	Johnson, Frank E.	Minneapolis
	Johnson, Franklin L.	Duluth
†	Johnson, Gerhard J.	Rochester
	Johnson, Gordon E.	Minneapolis
	Johnson, Harry A., Jr.	Minneapolis
	Johnson, Herbert W.	St. Paul
†	Johnson, James A.	Minneapolis
	Johnson, John W.	Minneapolis
	Johnson, Karl E.	Duluth
†	Johnson, Kenneth A.	Rochester
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	Johnson, Norman P.	Minneapolis
	Johnson, Norman Paul	St. Paul
	Johnson, Norton T.	Minneapolis
	Johnson, O. Guy	St. Paul
	Johnson, Olga H.	Moorhead
	Johnson, Paul E.	Wayzata
	Johnson, Ralph B.	Lanesboro
	Johnson, Reinald G.	Minneapolis
†	Johnson, Reuben A.	Minneapolis
	Johnson, Rex R.	New Ulm
	Johnson, Richard J.	St. Paul
	Johnson, Richard S.	Minneapolis
	Johnson, Robert E.	Minneapolis
	Johnson, Roger	Faribault
	Johnson, Theodore L.	Duluth
	Johnson, Thomas E.	St. Paul
†	Johnson, Thomas F.	Rochester
	Johnson, Thomas H., Jr.	Minneapolis
	Johnson, William E.	St. Cloud
	Johnson, William J.	Rochester
	Johnson, Youbert T.	Minneapolis
	Johnsrud, Luverne W.	Hibbing
#	Johnston, Bemis H.	Eatontown, NJ
	Johnston, Donald K.	Minneapolis
	Johnston, H. Wayne	Virginia
	Johnston, Leonard F.	Winona
†	Jones, Allen M.	Rochester
	Jones, David G.	Minneapolis
#	Jones, H. Royden, Jr.	APO New York, NY
†	Jones, Herbert W., Jr.	Minneapolis
	Jones, Richard H.	Minneapolis
†	Jones, Richard N.	St. Cloud
	Jordan, Donald V.	Minneapolis
†	Jordan, Kathleen B. Smith	Granite Falls
#	Jordan, James J.	Great Lakes, IL
	Jorgensen, Edward O.	Fergus Falls
	Jorgensen, Donald R.	St. Paul
	Jorgensen, Harlan	Minneapolis
	Joseph, Arnold H.	St. Paul
#	Joy, William B.	San Diego, CA
	Joyce, John W.	Rochester
	Judd, Allen S.	Minneapolis
	Judd, Edward S.	Rochester
	Judd, Walter H.	Washington, DC
†	Juergens, Herman M.	Belle Plaine
	Juergens, Manley F.	Stillwater
	Juers, Edward H.	Red Wing
	Juntunen, Roy R.	Duluth
	Jurdy, Mitchell	Minneapolis
	Just, Herman J.	Hastings
†	Juttner, Hans-Udo	Rochester

K

	Kadesky, Harold B.	Minneapolis
	Kaese, Werner E.	Rochester
	Kaiser, Harold B.	Minneapolis
	Kaiser, Milton L.	New Ulm
	Kalb, Thomas J.	Minneapolis
	Kallestad, Leonard L.	Wayzata
	Kane, Dennis J.	Minneapolis
	Kane, Morton C.	Minneapolis
	Kane, William J.	Minneapolis
	Kanne, Earl R.	Brainerd
†	Kantack, Paul W.	Rochester
	Kantar, Yale C.	St. Paul
	Kaplan, David H.	Edina
	Kaplan, Arnold P.	Minneapolis
	Kaplan, Harold A.	Minneapolis
	Kaplan, J. Jacob	Minneapolis
	Karges, Laurel E.	Grand Rapids
	Karish, Louis J.	Grand Rapids
	Karleen, Conrad I.	Minneapolis
	Karlen, Markle	Minneapolis
	Karn, Jacob F.	Ortonville
	Karnes, William E.	Rochester
	Karon, Everett H.	St. Paul
	Karon, Irvine M.	St. Paul
	Karrow, John W.	Granite Falls
†	Karsell, Philip R.	Rochester
†	Kasher, R. Jerome	Rochester
	Kasper, Eugene M.	St. Paul
	Kasper, Robert E.	Excelsior
	Kath, Reinhard H.	Arlington
	Katkov, Harold	Wayzata
	Katz, Beni	Minneapolis
#	Katz, Elliott S.	Portsmouth, VA
	Katz, Louis J.	Long Beach, CA
†	Kauderer, John G., Jr.	Rochester
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	Kavanaugh, Gerald J.	Rochester
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	Kearney, R. Wynn	Mankato
†	Kearney, R. Wynn, Jr.	Rochester
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	Keith, Haddow M.	Rochester
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	Keithahn, Elmer E.	Sleepy Eye
	Kelalis, Panayotis P.	Rochester
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	Kelly, Albert C.	St. Paul
	Kelly, Charles F.	Minneapolis
	Kelly, Edward H.	St. Paul
	Kelly, Helen M.	St. Paul
	Kelly, James H.	St. Cloud
	Kelly, John C.	Minneapolis
	Kelly, John F.	Cold Spring
	Kelly, John P.	Minneapolis
	Kelly, John T.	Minneapolis
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	Kelly, Patrick J.	Rochester
	Kelly, Robert T.	Grand Rapids
	Kelly, William D.	Minneapolis
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	Kelsey, Chauncey M.	St. Paul
†	Kemp, Alphonse F.	Mankato

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	Kennedy, William R.	Minneapolis
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	Kerr, Frederick W. L.	Rochester
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	Kevern, Jay L.	Henning
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	Kierland, Robert R.	Rochester
	Kiesler, Frank	Grand Rapids
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	Kilen, Mark B.	Duluth
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	Kippen, Neil	Breckenridge
	Kirby, Thomas J., Jr.	Rochester
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	Kitchen, Clyde K.	Minneapolis
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	Knip, Robert J.	Ortonville
	Knipp, William J.	Brainerd
	Knobloch, William H.	Minneapolis
	Knoche, Harvey A.	Gaylord
	Knoedler, John P.	Duluth
	Knoll, W. V.	Brainerd
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	Knutson, Robert C.	St. Paul
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	Kohlhase, Robert E.	Minneapolis
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	Koller, Robert L.	Minneapolis
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	Koons, William R.	Mahnomen
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	Koos, Gerald W.	Minneapolis
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	Korda, Henry A.	Pelican Rapids
	Koropchak, Nikolai	Minneapolis
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	Kosiak, William	Two Harbors
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	Kruger, E. Larry	Nashwauk
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†	Kucera, William J.	Santa Barbara, CA
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	Kuhlmann, Vernon G.	Alexandria
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	Kulzer, Norbert J.	Hastings
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	Kusske, Douglas R.	St. Paul
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	Kvale, Walter F.	Rochester
	Kvam, Lowell L.	St. Paul
	Kvamme, Brynjulv	Mabel

	Kvistberg, Gerald K.	St. Cloud
	Kwako, Jerome E.	Duluth
	Kyle, Robert A.	Rochester
	Kyllo, John E.	Minneapolis

L

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	LaBree, Robert H.	Duluth
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	Larsen, Frank W.	Minneapolis
	Larsen, Russel H.	Lakefield
	Larson, Arthur K.	Minneapolis
	Larson, Donald Marvin	Minneapolis
	Larson, Donald Myren	Duluth
	Larson, Dorette W.	Fergus Falls
	Larson, Ernest J., Jr.	Minneapolis
	Larson, Eva Jane O.	St. Paul
	Larson, F. Wilmer	Minneapolis
	Larson, Gerald E.	Cambridge
	Larson, Jerrold V.	St. Paul
	Larson, Keith D.	Medical Lake, WA
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	Larson, Leighton W.	Waconia
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	Larson, Richard E.	Minneapolis
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	Larson, Roger C.	Minneapolis
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	Larson, Theodore G.	Brainerd
	Larson, Wyllis G.	Minneapolis
	Laszewski, Franz von Zelberschwecht	St. Paul
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	Latts, Elliot M.	Minneapolis

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	Lawrence, Van S.	Minneapolis
	Lawrow, John W.	Minneapolis
	Lawson, Warren R.	Minneapolis
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	Lee, Hubert W.	Brainerd
	Lee, Norman J.	Tracy
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	Lee, Robert E.	Rochester
	Lee, William C.	Hibbing
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	Lees, Jack R.	St. Paul
	Lehman, Donald S.	St. Paul
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	Leighton, John S.	Minneapolis
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	Leitch, Cecil M.	Litchfield
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	Lenander, Mellvin E. L.	St. Peter
	Lenarz, Albert J.	St. Cloud
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	Lenz, Oa	Minneapolis
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	Leonard, Samuel	Minneapolis
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	Leslie, W. Robert	Minneapolis
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	Lester, Theodore H.	Minneapolis
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	Loes, Louis A.	St. Cloud
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	Lufkin, Nathaniel H.	Minneapolis
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	Mach, Ralph F.	Pine City
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	Mackoff, Samuel	Phoenix, AZ
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	Mahle, James P.	Minneapolis
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	Malkasian, George D.	Rochester
	Malmquist, Carl P.	Minneapolis
	Mandel, Sheldon L.	Minneapolis
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	Marking, George H.	Minneapolis
	Markland, A. Colin	Minneapolis
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	Marta, John B.	St. Paul

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	Martens, Theodore G.	Rochester
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	Martin, David E., III	Wabasha
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	Martin, Dwight L.	St. Paul
	Martin, Frank E.	Minneapolis
	Martin, Frederick F.	Bagley
	Martin, George B.	Thief River Falls
	Martin, George R.	Minneapolis
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	Masson, James K.	Rochester
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	Mathews, Wallace E.	Mankato
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	Mueller, LeRoy E.	Hendricks
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	Myre, Clifford R.	Paynesville

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†	Nadeau, Claude	Trois-Rivieres, Quebec, Canada
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	Nagobads, V. George	Minneapolis
	Najarian, John S.	Minneapolis

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†	Nathan, Fred F.	Rochester
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	Nealy, Timonty E.	Blooming Prairie
	Neary, Richard P.	Minneapolis
	Neault, Roger W.	Rochester
	Neel, Harry B.	Albert Lea
	Neff, Walter S.	Virginia
	Neher, Frederick J.	St. Paul
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	Nelson, C. Barton	Minneapolis
	Nelson, Carleton A.	Minneapolis
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	Nelson, David J.	Minneapolis
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†	Nelson, J. Phillip	Rochester
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	Nelson, Louis A.	St. Paul
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	Nelson, Maynard C.	Minneapolis
	Nelson, O. L. Norman	Minneapolis
	Nelson, Robert H.	Benson
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	Nelson, Roy A.	Fergus Falls
	Nelson, Wallace I.	Minneapolis
	Nerenberg, Sidney	Minneapolis
	Nesheim, Martin O.	Emmons
	Ness, Duane E.	Wadena
	Ness, Richard A.	Fergus Falls
	Nesset, Lawren B.	Minneapolis
	Nesset, William D.	Minneapolis
	Nesvacil, Leon	St. Paul
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	Neumann, Roland F.	Minneapolis
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	Neuwirth, Gerardo D.	Minneapolis
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	Nicholson, Richard W.	Fergus Falls
	Nickerson, John R.	Fairmont
	Nickerson, Neil D.	Fairmont
	Nicolay, William R.	Red Wing
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	Nywall, Dean D.	Slayton

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	Odland, Olin M.	Granite Falls

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	Officer, Charles D.	Burnsville
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	Orandi, Mehdi	Fergus Falls
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	Payne, W. Spencer	Rochester
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Phelps, Robert D. .... Minneapolis
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Philp, David R. .... Watertown
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Pierre, Robert V. .... Rochester
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Pilling, Loran F. .... Minneapolis
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Pivac, Dragojla (Popovich) .... Milwaukee, WI
Pizarro, Remi L. .... Minneapolis
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Plass, Herbert F. R. .... Minneapolis
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† Plummer, Leo J. .... Rochester
† Pluth, James R. .... Rochester
Pohl, John F. .... Minneapolis
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Poston, Lawrence M. .... Caledonia
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Powers, Robert L. .... St. Paul
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Provence, Cecil L. .... Waconia
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Pugh, David G. .... Rochester
Pulec, Jack Lee .... Rochester
Pumala, Erven E. .... Warren
Purnell, Don C. .... Rochester
Purves, G. Harland .... Buffalo
Puumala, Barbara M. .... Cloquet
Puumala, Reino H. .... Cloquet
Puumala, Ricard R. .... Cloquet

Q

	Quattlebaum, Frank W.	St. Paul
	Quello, Robert O. B.	Minneapolis
	Quiggle, Arthur B.	Minneapolis
	Quist, Henry W., Jr.	Minneapolis

R

	Raab, David E.	Minneapolis
	Raaen, Olaf J.	St. Paul
	Rabcevich, Anatole	St. Paul
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	Raetz, Sylvester J.	Maple Lake
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	Randall, Raymond V.	Rochester
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	Reeber, Erick	Bagley
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	Rholl, Arnold O.	Minneapolis
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	Rice, Carl O.	Minneapolis
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	Rice, Fred A.	Minneapolis
	Rice, Hagbart G.	Moorhead
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	Russ, Homer H., Jr.	Warroad
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S

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	Salovich, Edward L.	Minneapolis
	Salovich, Elmer R.	Minneapolis
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	Salter, Reginald A.	Virginia
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	Sand, Richard E.	St. Paul
	Sandeen, Robert M.	Buffalo
	Sander, Frank V., Jr.	Rochester
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	Sanderson, David R.	Rochester
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	Sandt, Karl E.	La Jolla, CA
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†	Sanfilippo, Sylvester J.	Minneapolis
	Sanford, John B.	Duluth

	Sanford, Raymond A.	Mankato
†	Santoscoy, Gilbert S.	Rochester
	Sargent, John H.	St. Paul
	Sartor, Richard	Minneapolis
	Sather, Edgar L.	Fosston
	Sather, George A.	Fosston
	Sather, Richard N.	Fosston
†	Sather, Russell A.	Dallas, TX
	Sather, Russell O.	Crookston
†	Sato, Kazuyoshi	Rochester
†	Sauer, Jean C.	Ft. Snelling
	Sauer, Robert L.	Preston
	Sauer, William G.	Rochester
	Savaryn, John P.	Waconia
	Savelkoul, Gene R.	Belgrade
	Sawtell, Robert R.	Rochester
	Sax, Milton H.	Duluth
	Sax, Simon G.	Duluth
	Saxman, Gertrude E. O.	Ulen
	Sayre, George P.	Rochester
	Sayther, Keith D.	Minneapolis
	Sborov, Abe M.	Minneapolis
	Scallen, Raymond W.	Minneapolis
	Scanlan, Patrick J.	Minneapolis
	Scanlon, Hugh A.	Little Falls
	Scanlon, Paul W.	Rochester
	Schaar, Frances E.	Minneapolis
†	Schade, Frederick L.	Santa Cruz, CA
†	Schaefer, Joseph F.	Owatonna
	Schaefer, Wesley G.	Minneapolis
	Schafer, Charles F.	Winona
	Schaffhausen, George E.	St. Paul
	Schaffhausen, Irwin F.	Minneapolis
	Schaffhausen, Mildred	Minneapolis
	Schamber, Walter F.	St. Cloud
	Schattenberg, Thomas T.	Rochester
	Scheidel, Alois M.	Mankato
	Scherek, Jerome J.	St. Paul
	Scherer, L. Raymond	Minneapolis
	Scherling, Sidney S.	Minneapolis
	Schiele, Burtrum C.	Minneapolis
	Schimelpfenig, George T.	Chaska
	Schirber, Martin J.	Grand Rapids
	Schirger, Alexander	Rochester
	Schissel, Gregory A.	Minneapolis
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	Schloff, Ivan	St. Paul
	Schloff, Leonard D.	St. Paul
	Schmid, John F.	Duluth
†	Schmidt, Hilmar R.	Winona
	Schmidt, Paul G.	Granite Falls
	Schmidt, Ruben F.	Alden
	Schmidt, W. Robert	Minneapolis
	Schmidtke, Reinhardt L.	Minneapolis
†	Schmitt, S. C.	Fallbrook, CA
	Schmitz, Anthony A.	Mankato
	Schmitz, Everett J.	St. Cloud
	Schnabel, Norma B.	Crookston
	Schnabel, Robert F.	Crookston
	Schneck, Jack I.	Minneapolis
	Schneider, Lawrence E.	Duluth
	Schneider, Paul J.	Adams
	Schnell, Frederick S.	Litchfield
†	Schnur, Paul L.	Rochester
†	Schoch, Robert B. J.	St. Paul
	Schochet, H. Laurence	St. Paul
†	Schoen, Roland F.	Rochester
	Schoeneberger, P. B.	Perham
	Schoenfield, Leslie J.	Rochester
	Schoening, Herbert A.	Minneapolis
	Schoenwetter, William F.	Minneapolis
	Scholz, Donald A.	Rochester
†	Schons, Edward	Minnetonka Beach
	Schossow, George W.	White Bear Lake
#	Schottler, Jerry L.	Minneapolis
	Schottler, Max E.	Minneapolis
	Schotzko, John R.	Blue Earth
	Schrader, Wayne H.	St. Paul
	Schrantz, Robert D.	Rochester
	Schroeckenstein, Hugo F.	St. Paul
	Schroeder, Albert J.	Minneapolis
	Schroeder, Glenn E.	Red Wing
	Schroeppel, John E.	Winthrop
	Schulberg, Verne A.	Minneapolis
	Schultz, Alan K.	Minneapolis
	Schultz, Alvin L.	Minneapolis
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	Schultz, J. Harold	Minneapolis
	Schultz, Peter J.	Minneapolis
	Schultz, Robert J.	Minneapolis
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	Schulze, William M.	Minneapolis
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	Schumacher, Robert V.	Minneapolis
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	Schut, Lawrence J.	Minneapolis
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	Schwartz, E. Robert	Minneapolis
	Schweiger, Theodore R.	Hibbing
	Scott, Eugene E.	St. Paul
	Scott, Horace G.	Minneapolis
	Scott, Robert H.	Minneapolis
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	Scudamore, Harold H.	Rochester
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	Searl, Richard H.	Faribault
	Seay, James E., III	Minneapolis
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	Sedlack, Richard E.	Rochester
	Seecamp, Carsten H.	Cambridge
	Segal, Edward L.	Minneapolis
	Segal, Martin A.	Minneapolis
	Segal, Marvin S.	Minneapolis
	Segal, Sheldon J.	Minneapolis
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†	Seham, Max	St. Paul
	Seibel, David I.	Minneapolis
	Seifert, Donald R.	Little Falls
	Seifert, Milton H.	Excelsior
	Seifert, Milton H., Jr.	Excelsior
	Seisler, Edward P.	Worthington
	Sekhon, Mohan S.	St. Paul
	Seldon, Thomas H.	Rochester
	Seljeskog, Edward L.	Minneapolis
	Sells, Richard J.	St. Paul
	Selmo, Joseph D.	Norwood
	Semba, Thomas	Minneapolis
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	Semsch, Robert D.	Wayzata
†	Service, Frederick J.	Rochester
	Sessler, Alan D.	Rochester
	Sethre, Arthur E.	Fergus Falls
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	Setzer, Hobert J., Jr.	Mankato
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	Shandorf, James F.	Minneapolis

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	Shapiro, Sidney K.	Minneapolis
	Shapiro, Stanley W.	Minneapolis
	Shattuck, Clark A.	Minneapolis
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	Shaw, Howard A.	Minneapolis
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	Shelander, Marcus I.	St. Paul
	Shemesh, Alvin	Minneapolis
	Shepard, Richard	Albert Lea
	Sheppard, Charles G.	St. Peter
	Sheps, Sheldon G.	Rochester
	Sher, David A.	Virginia
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	Sherman, Alfred G.	Albert Lea
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	Sherman, Charles L.	Luverne
	Sherman, Lloyd F.	Minneapolis
	Sherman, Royal V.	Red Wing
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†	Shillington, Maurice A.	Ft. Lauderdale, FL
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	Shin, Rok	Howard Lake
	Shirley, Raymond M.	Duluth
	Sholler, Lawrence J.	Minneapolis
	Short, Marshall H.	St. Paul
	Shragg, Robert I.	Minneapolis
	Shronts, John F.	Minneapolis
	Sidell, Franklin D.	Minneapolis
	Siebert, Darrell W.	Luverne
	Siegel, Clarence	St. Paul
	Siegel, John S.	Virginia
	Siegmann, William C.	Minneapolis
	Siekert, Robert G.	Rochester
	Sigel, Melvin E.	Minneapolis
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	Silver, John D.	Minneapolis
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	Silverstein, Murray N.	Rochester
	Silverstein, Paul M.	Minneapolis
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	Simmonds, Harry N. L.	St. Paul
	Simmons, Richard K.	Minneapolis
	Simo, Kathleen Kay	Minneapolis
	Simons, John N.	Rochester
	Simons, Leander T.	St. Paul
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	Simpson, Thomas E.	Rochester
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	Sjostrom, Lawrence E.	St. Peter
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	Skaug, Harold M.	Chatfield
	Skinner, Abbott	St. Paul
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	Slack, William J.	Duluth
	Slanga, Roger A.	St. Cloud
	Slocumb, Charles H.	Rochester
	Slosser, Gaius J.	Minneapolis
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	Smiley, John T.	Minneapolis
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†	Smisek, Frank M.	Minneapolis
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	Smith, Archie M.	Minneapolis
	Smith, Barlow	Minneapolis
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	Smith, Don V.	Blue Earth
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	Smith, Graham G.	Minneapolis
	Smith, H. Nippert	St. Paul
	Smith, Harry J.	Lake Crystal
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	Smith, Lucian A.	Rochester
	Smith, Nadine G.	Minneapolis
	Smith, Ralph E.	Rochester
	Smith, Reginald A.	Rochester
	Smith, Theodore S.	Minneapolis
	Smith, Vernon D. E.	St. Paul
	Smith, Wallace R.	Grand Marais
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	Smythe, Lowell J.	Austin
	Snider, Howard R.	Mankato
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	Snyker, Omer E.	Ely
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†	Soltani, Johanguir	Rochester
	Solvason, Harold M.	Minneapolis
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	Sommerdorf, Vernon L.	St. Paul
	Sommers, Stephen D.	St. Cloud
	Sones, Donald A.	Rochester
	Sonnesyn, Nels N.	Le Sueur
	Sontag, David W.	Lake City
	Sorem, Milton B.	St. Paul
	Soriano, Dominador B.	Onamia
	Soucheray, Philip H.	St. Paul
	Soule, Edward H.	Rochester
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	Sowada, Ernest J.	St. Paul
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	Spain, W. Thomas	Evansville, IN
	Spang, Anthony J.	Duluth

	Spang, James S.	Duluth
	Spang, William M.	Duluth
	Spano, Joseph P.	Minneapolis
	Spencer, Bernard J.	Minneapolis
	Spencer, David L.	Anoka
	Spencer, Robert J.	Rochester
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	Spieler, F. B.	Pequot Lakes
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	Spink, Wesley W.	Minneapolis
	Spittell, John A., Jr.	Rochester
	Sponsel, Kenath H.	Minneapolis
	Sporre, Knute A.	Fergus Falls
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	Sprafka, Joseph L.	St. Paul
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	Spraitz, Anton F., Jr.	St. Paul
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	Stafne, John G.	St. Paul
	Stahl, George W.	Austin
	Stahn, Louis H.	St. Cloud
	Stahr, Aubrey C.	Hopkins
	Stam, John	Worthington
†	Stanford, Charles E.	Elcho, WI
†	Stanley, Court R.	Minneapolis
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	Staub, Henry P.	Minneapolis
†	Stauffer, Maurice H.	Rochester
†	Stauffer, Richard N.	Rochester
#	Stecker, Raymond H.	APO New York, NY
†	Steffens, Leon A.	Red Wing
	Steidl, Richard M.	Minneapolis
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	Stein, Raymond J.	Pierz
	Stein, Robert L.	North St. Paul
	Stein, William A.	Duluth
	Steinberg, Charles L.	St. Paul
	Steiner, Andrew M.	St. Michael
	Steiner, Leon E.	Albert Lea
†	Steinfeld, Carroll M.	Rochester
	Steinhilber, Richard M.	Rochester
	Stelter, Lloyd A.	Minneapolis
	Stemsrud, Harold L.	Alexandria
	Stengl, Thomas A.	St. Paul
#	Stenseth, Jon H.	APO, NY
†	Stenstrom, Annette T.	Grand Marais
	Stenzel, Donald A.	Minneapolis
	Stenzel, Joseph A.	Minneapolis
	Stephens, William E.	Minneapolis
†	Sterling, William A.	Rochester
†	Stern, Barry L.	Rochester
	Sterner, Donald C.	St. Paul
	Sterner, Ernest R.	St. Paul
	Sterner, John J.	St. Paul
	Sterrie, Norman A.	Minneapolis
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	Stewart, Donald E.	Crookston
#	Stewart, James R.	El Paso, TX
	Stewart, Marvin J.	Minneapolis
	Stewart, Paul B.	Minneapolis
	Stickney, J. M.	Rochester
	Stiegler, Farrell S.	Minneapolis
	Stifter, Anton J.	Winsted
	Stiles, Clifford D.	Foley
	Stillwell, George K.	Rochester
	Stillwell, Walter C.	Mankato
	Stilwell, George G.	Rochester
	Stoesser, Albert V.	Minneapolis
	Stoker, Lynn C.	Albert Lea
#	Stolee, Curtis N.	Fort Dauphin, Madagascar
	Stolee, Thomas A.	St. Paul
	Stolen, Keith H.	Grand Rapids
	Stoltz, Robert C.	Minneapolis
	Stone, Norman F.	Minneapolis
	Stone, Stanley P.	Minneapolis
	Storsteen, Kenneth A.	Duluth
	Stover, Laddie E.	Marshall
	Stoy, Robert A.	Little Falls
	Strait, Herbert S.	Minneapolis
	Strand, Clarence M.	Minneapolis
	Strand, Jack W.	Jasper
	Stransky, Theodore W.	Owatonna
	Strathern, Carleton S.	St. Peter
†	Stratte, Alf K.	Pine City
†	Stratte, Harold C.	Windom
	Stratte, Jon R.	Stillwater
	Strauchler, John	Belview
	Straus, Maurice L.	St. Paul
	Street, Bernard	Northfield
	Streitz, John M.	Duluth
	Strem, Edward L.	St. Paul
	Streu, Richard E.	Minneapolis
	Strewler, Gordon J.	Duluth
	Strickland, Martha J. B.	Minneapolis
	Strickler, Jacob H.	Minneapolis
	Strobel, Claire J. A.	Mankato
	Strobel, Jack L.	Minneapolis
	Stroebel, Charles F., Jr.	Rochester
	Strom, Gordon W.	Minneapolis
	Strom, Robert L.	Minneapolis
	Stromgren, Delph T.	Minneapolis
	Stromme, William B.	Minneapolis
	Strong, Cameron G.	Rochester
	Strough, La Vern C.	Worthington
	Strunk, Clarence A.	Minneapolis
	Struthers, Lewis	Parkers Prairie
†	Stubbs, Samuel E.	Rochester
	Student, Richard E.	Minneapolis
	Studer, Donald J.	Faribault
*†	Stuhr, John W.	Stillwater
	Sturges, Robert L.	Minneapolis
	Sturley, Rodney F.	St. Paul
	Subak, Barbara H.	Minneapolis
	Subby, Walter	Minneapolis
	Sukov, Marvin	Minneapolis
	Sulciner, Aurel	Minnetonka
	Sullivan, W. Albert, Jr.	St. Paul
	Summar, M. Thomas	Virginia
	Summerskill, William H.	Rochester
	Sundberg, A. Bruce	Minneapolis
†	Suros, Juan	Rochester
†	Sutthivan, Phaibul	Rochester
#	Sutherland, John E.	Indian Head, MD
†	Sutor, Anton H.	Rochester
	Svien, Hendrik J.	Rochester
†	Svoboda, Wm. B.	Rochester
	Swaiman, Kenneth F.	Minneapolis
	Swallen, Thomas O.	Minneapolis
†	Swanson, David A.	Minneapolis
	Swanson, John O.	Minneapolis
	Swanson, Lawrence J.	West St. Paul
	Swanson, Ralph H.	West St. Paul
	Swedberg, William A.	Duluth
	Swedenburg, Paul A.	Glenwood
	Sweetser, Horatio B.	Minneapolis

	Sweetser, Theodore H., Jr.	Minneapolis
	Swendseen, Carl J.	Minneapolis
†	Swendson, James J.	St. Paul
	Swensen, Don P.	Duluth
	Swenson, Arnold O.	Duluth
	Swenson, Donald B.	St. Paul
	Swenson, Donald B.	Mankato
	Swenson, Floyd J.	Grand Rapids
	Swenson, James D.	Edina
	Swenson, Orvie J.	Waseca
	Swenson, Orville P.	Cloquet
	Swenson, Richard W.	Minneapolis
	Swenson, Roy G.	North Branch
	Swift, Dean C.	Minneapolis
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	Symmonds, Richard E.	Rochester
	Syverson, Leslie A.	Fergus Falls

T

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	Taintor, Ronald W.	Marshall
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	Tanaka, Shin	Minneapolis
	Tanasichuk, Murray A.	St. Paul
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	Teisberg, John E.	St. Paul
	Tenner, Robert J.	Minneapolis
	Terrell, Bernard J.	Nopeming
	Teska, Byron A.	Minneapolis
	Testor, James V.	Winona
	Tetlie, James P.	Duluth
	Teynor, Joseph W.	Minneapolis
	Tharp, Ralph	Minneapolis
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	Theobalt, Inge M.	Minneapolis
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	Thiem, Chester E.	Mankato
	Thienes, R. Lawrence	St. Cloud
	Thomas, John V.	Duluth
	Thomas, Juergen E.	Rochester
	Thomas, William H.	Minnetonka
	Thomasson, Robert D.	Minneapolis
	Thomes, A. Boyd	Minneapolis
	Thompson, Arthur	Minneapolis
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	Thompson, Carl O.	Hendricks
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	Thompson, Russell A.	Willmar
	Thompson, Wayne W.	St. Paul
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	Thorp, William B.	Minneapolis
	Thorsgard, Ernest O.	Thief River Falls
	Thorson, Stuart V.	Minneapolis
	Thurber, Deloran L.	Rochester
	Thuringer, Carl B.	St. Cloud
	Thurn, Roy J.	Duluth
	Thysell, Desmond M.	Minneapolis
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	Tifft, Cyril R.	St. Paul
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	Titrud, Leonard A.	Minneapolis
	Titus, Jack L.	Rochester
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	Tobin, John D.	Minneapolis
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	Todd, John C.	Austin
	Toft, Thomas V.	Rochester
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	Torres, Fernando	Minneapolis
	Tosseland, Noel E.	Duluth
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	Turkbas, Nejat	St. Paul
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	Tveten, Omar A.	St. Paul

	Tweedy, John A.	Winona
	Tweedy, Robert	Winona
	Twidwell, Joseph E.	Minneapolis
	Twiggs, Leo F.	Austin
	Tyce, Francis A.	Rochester

U

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	Undem, Dale	Alexandria
	Underdahl, Laurentius O.	Rochester
	Utendorfer, Robert W.	Minneapolis
	Utz, David C.	Rochester

V

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†	Van Dervoort, Robert L., Jr.	Rochester
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	Van Herik, Martin	Rochester
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	Van Ryzin, Donald J.	Duluth
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	Vaughn, Louis D.	Rochester
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	Verby, John E.	Bloomington
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	Virnig, Mark P.	Wells
	Virnig, Richard P.	Wells
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	Vollmer, Frederick J.	Winona
	Von Drashek, Stanley C.	Minneapolis
	Vorlicky, Loren N.	Minneapolis
	Votel, Thomas W.	St. Paul

W

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	Wagner, Norman W.	Benson
	Wagner, Robert M.	Minneapolis
	Wagoner, Richard D.	Rochester
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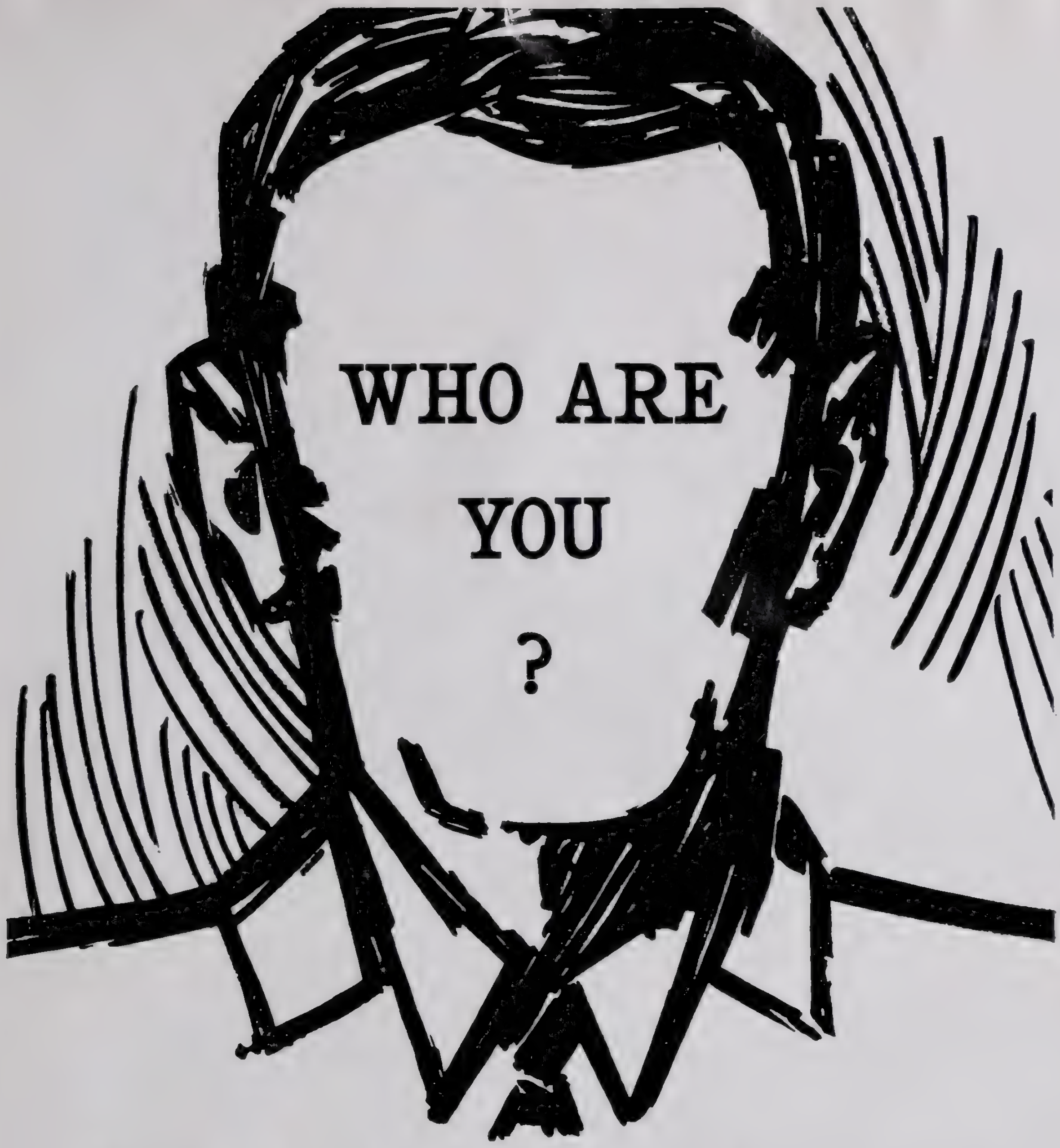

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BLUE SHIELD
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Whenever anxiety induces or intensifies clinical symptoms

Librium®

(chlordiazepoxide HCl)

Quickly relieves anxiety ~ Helps improve response in psychophysiologic disorders ~ Seldom impairs mental acuity or physical coordination, on proper dosage ~ Has wide margin of safety

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Indicated when anxiety, tension and apprehension are significant components of the clinical profile.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

Usual Daily Dosage: Individualize for maximum beneficial effects. *Oral*—Adults: Mild and moderate anxiety and tension, 5 or 10 mg t.i.d. or q.i.d.; severe states, 20 or 25 mg t.i.d. or q.i.d. Geriatric patients: 5 mg b.i.d. to q.i.d. (See Precautions.)

Supplied: Librium® (chlordiazepoxide HCl) Capsules, 5 mg, 10 mg and 25 mg—bottles of 50. Libritabs™ (chlordiazepoxide) Tablets, 5 mg, 10 mg and 25 mg—bottles of 100. With respect to clinical activity, capsules and tablets are indistinguishable.

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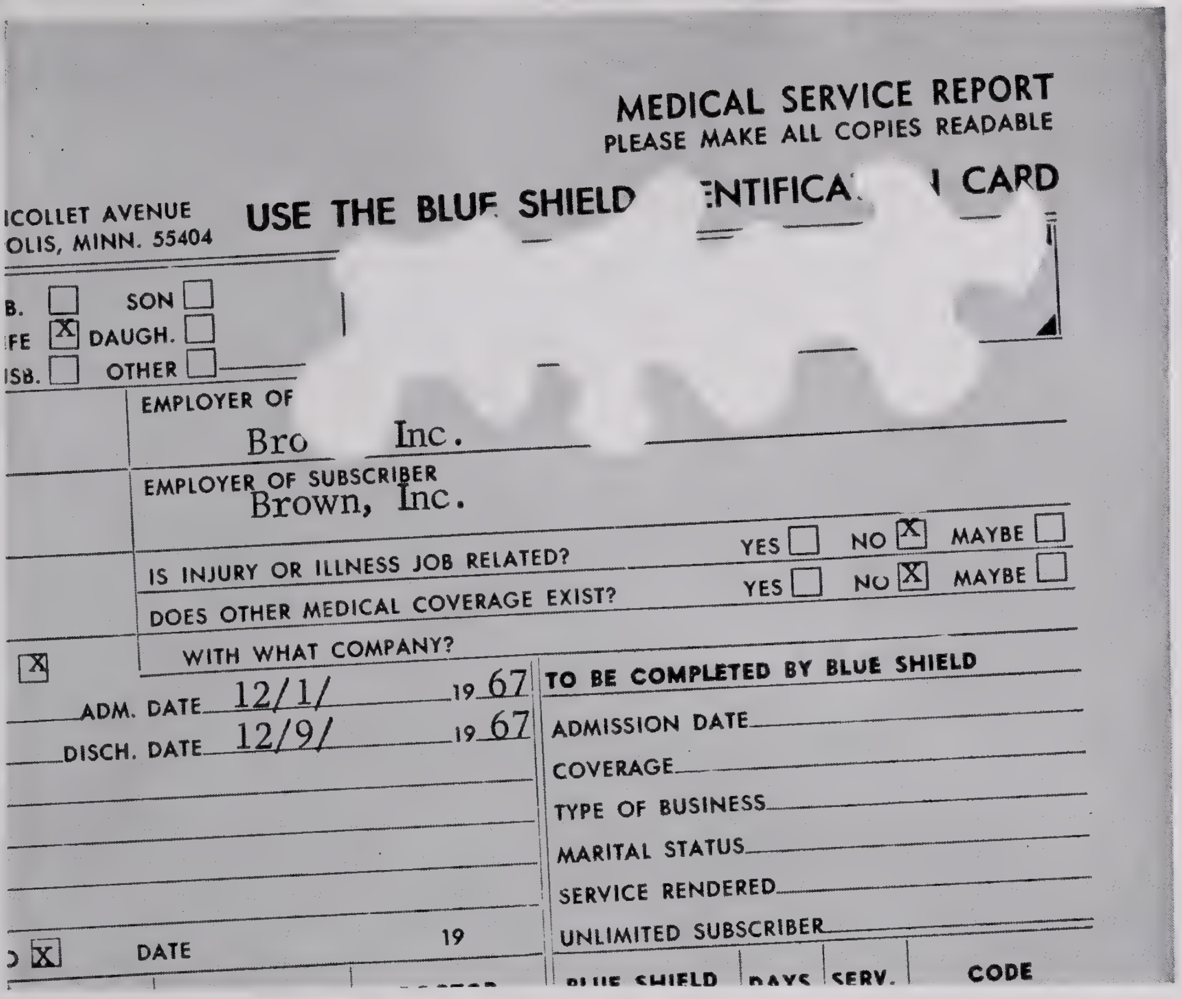
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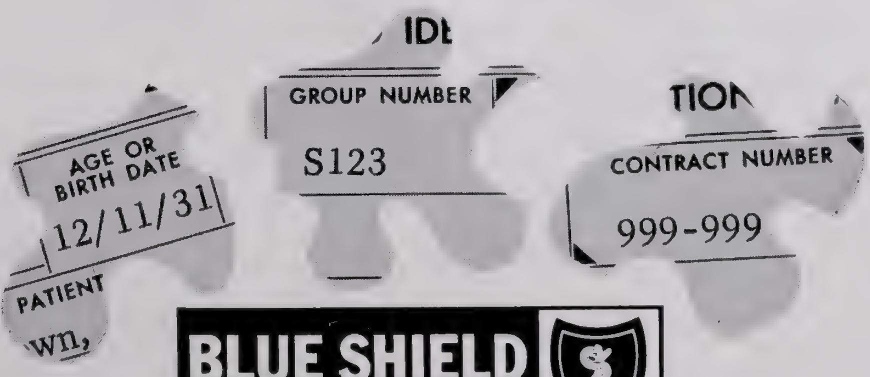
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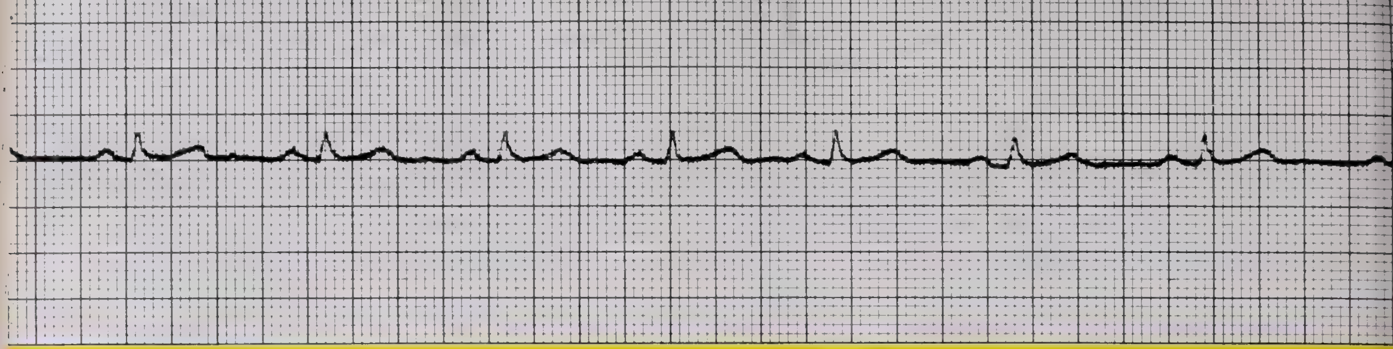

When disease is ruled out and psychic tension is implicated

Valium® (diazepam)

helps relax the patient and relieve his somatic symptoms

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms have occurred following abrupt discontinuance. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation, have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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Thomas J. Kinsella, M.D.

JULY, 1969

Dear Doctor,
You made me
what I am today-
a whole lot
slimmer!

TEPANIL—the right start in support of the weight-control program *you* recommend. It reduces the appetite. Doesn't kill it. Weight loss is significant—gradual—yet there is a relatively low incidence of CNS stimulation. Because TEPANIL works on the appetite, not on the "nerves."

Contraindications: Concurrently with MAO inhibitors, in patients hypersensitive to this drug; in emotionally unstable patients susceptible to drug abuse.

Warning: Although generally safer than the amphetamines, use with great caution in patients with severe hypertension or severe cardiovascular disease. Do not use during first trimester of pregnancy unless potential benefits outweigh potential risks.

Adverse Reactions: Rarely severe enough to require discontinuation of therapy, unpleasant symptoms with diethylpropion hydrochloride have been reported to occur in relatively low incidence.

As is characteristic of sympathomimetic agents, it may occasionally cause *CNS effects* such as insomnia, nervousness, dizziness, anxiety, and jitteriness. In contrast, CNS depression has been reported. In a few epileptics an increase in convulsive episodes has been reported.

Sympathomimetic *cardiovascular effects* reported include ones such as tachycardia, precordial pain, arrhythmia, palpitation, and increased blood pressure. One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride; this was an isolated experience, which has not been reported by others.

Allergic phenomena reported include such conditions as rash, urticaria, ecchymosis, and erythema.

Gastrointestinal effects such as diarrhea, constipation, nausea, vomiting, and abdominal discomfort have been reported.

Specific reports on the hematopoietic system include two each of bone marrow depression, agranulocytosis, and leukopenia.

A variety of miscellaneous adverse reactions have been reported by physicians. These include complaints such as dry mouth, headache, dyspnea, menstrual upset, hair loss, muscle pain, decreased libido, dysuria, and polyuria.

Convenience of two dosage forms: TEPANIL Ten-tab tablets: One 75 mg. tablet daily, swallowed whole, in midmorning (10 a.m.); TEPANIL: One 25 mg. tablet three times daily, one hour before meals. If desired, an additional tablet may be given in midevening to overcome night hunger. Use in children under 12 years of age is not recommended.

Tepanil® Ten-tab®
(continuous release form)
(diethylpropion hydrochloride)

THE NATIONAL DRUG COMPANY
DIVISION OF RICHARDSON-MERRELL INC.
PHILADELPHIA, PENNSYLVANIA 19144 T-818A U.S. PATENT NO. 3,001,910 5/69

LACTINEX®

TABLETS & GRANULES

■ to help restore and stabilize the intestinal flora

■ for fever blisters and canker sores of herpetic origin

Lactinex contains both *Lactobacillus acidophilus* and *L. bulgaricus* in a standardized viable culture, with the naturally occurring metabolic products produced by these organisms.

Lactinex has been shown to be useful in the treatment of gastrointestinal disturbances, and for relieving the painful oral lesions of fever blisters and canker sores of herpetic origin.[1,2,3,4,5,6,7,8]

No untoward side effects have been reported to date.

Literature on indications and dosage available on request.

HYNSON, WESTCOTT & DUNNING, INC.

Baltimore, Maryland 21201

(LX-O5)

References:

(1) Siver, R. H.: CMD, *21*:109, September 1954. (2) Frykman, H. H.: Minn. Med., *38*:19-27, January 1955. (3) McGivney, J.: Tex. State Jour. Med., *51*:16-18, January 1955. (4) Quehl, T. M.: Jour. of Florida Acad. Gen. Prac., *15*:15-16, October 1965. (5) Weekes, D. J.: N.Y. State Jour. Med., *58*:2672-2673, August 1958. (6) Weekes, D. J.: EENT Digest, *25*:47-59, December 1963. (7) Abbott, P. L.: Jour. Oral Surg., Anes., & Hosp. Dental Serv., 310-312, July 1961. (8) Rapoport, L. and Levine, W. I.: Oral Surg., Oral Med. & Oral Path., *20*:591-593, November 1965.

He is a diabetic.
He is middle-aged.
When he needs an antibiotic
he may be a candidate for

DECLOSTATIN® 300 b.i.d.

Demethylchlortetracycline HCl 300 mg
and Nystatin 500.000 units
CAPSULE-SHAPED TABLETS Lederle

To guard susceptible patients against intestinal monilial overgrowth during broad-spectrum therapy—the protection of nystatin is combined with demethylchlortetracycline in DECLOSTATIN.

For your susceptible candidates, prescribe DECLOSTATIN—the broad-spectrum therapy that prevents monilial overgrowth.

Effectiveness: Because its antibacterial component is DECLOMYCIN Demethylchlortetracycline, DECLOSTATIN should be equally or more effective therapeutically than other tetracyclines in infections caused by tetracycline-sensitive organisms. The antifungal component, Nystatin, protects against superinfection by antibiotic-resistant fungal overgrowth (particularly monilia) in the intestinal tract.

Contraindication: History of hypersensitivity to demethylchlortetracycline or nystatin.

Warning: In renal impairment, usual doses may lead to excessive accumulation and liver toxicity. Under such conditions, lower than usual doses are indicated, and, if therapy is prolonged, serum level determinations may be advisable. A photodynamic reaction to natural or artificial sunlight has been observed. Small amounts of drug and short exposure may produce an exaggerated sunburn reaction which may range from erythema to severe skin manifestations. In a smaller proportion, photoallergic reactions have been reported. Patients should avoid direct exposure to sunlight and discontinue drug at the first evidence of skin discomfort. Necessary subsequent courses of treatment with tetracyclines should be carefully observed.

Precautions: Overgrowth of nonsusceptible organisms may occur. Constant observation is essential. If new infections appear, appropriat measures should be taken. In infants, increased intracranial pressur with bulging fontanels has been observed. All signs and symptoms hav disappeared rapidly upon cessation of treatment.

Side Effects: Gastrointestinal system—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. Skin—maculopapular and erythematous rashes; a rare case of exfoliative dermatitis ha been reported. Photosensitivity; onycholysis and discoloration of th nails (rare). Kidney—rise in BUN, apparently dose related. Transien increase in urinary output, sometimes accompanied by thirst (rare) Hypersensitivity reactions—urticaria, angioneurotic edema, anaphylaxis Teeth—dental staining (yellow-brown) in children of mothers given thi drug during the latter half of pregnancy, and in children given the dru during the neonatal period, infancy and early childhood. Enamel hypoplasia has been seen in a few children. If adverse reaction or idiosy crasy occurs, discontinue medication and institute appropriate therap Demethylchlortetracycline may form a stable calcium complex in an bone-forming tissue with no serious harmful effects reported thus fa in humans.

Average Adult Daily Dosage: 150 mg q.i.d. or 300 mg b.i.d. Should b given 1 hour before or 2 hours after meals, since absorption is impaire by the concomitant administration of high calcium content drugs, food and some dairy products. Treatment of streptococcal infections should continue for 10 days, even though symptoms have subsided.

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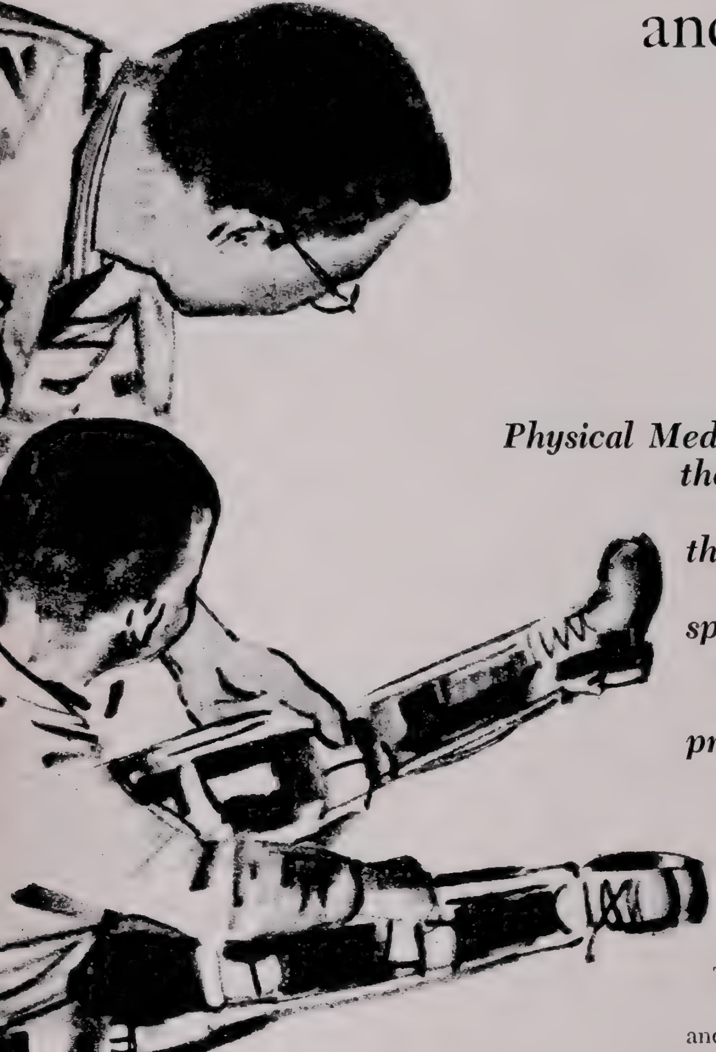

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Meet the Chairman

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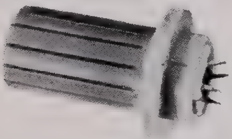

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Chairman's Letter

Health Care Programs

IN RECENT YEARS doctors have been the object of much attention from the government and the communication media of the country. The "Winds of Change" have been blowing hard upon us, urging us to "new solutions" for the goal of medical care for all. The most recent exposure for pediatricians has been as consultants in the Head Start Program. In the fall of 1967 the American Academy of Pediatrics signed a contract with the OEO to provide consultants for this program, and over 600 pediatricians across the country have accepted such assignments.

The 38 projects in Minnesota are covered by 14 Minnesota pediatricians. Those of us involved have found ourselves studying methods for providing medical care to selected groups of children, as outsiders in the community to which we were assigned, and in such role we have now received much information from the National Head Start office about how medical care for children might be accomplished. No one approach has been insisted upon, however; the consultants have been free to advise whatever they think best, depending on the particular individual situation.

A. Frederick North, Jr., M.D., former Senior Pediatrician, Project Head Start, Office of Economic Opportunity, in a communication to Head Start consultants, has recently listed the problems in establishing a health care program for a group of children in a Head Start project as including the identification of "the preventive and restorative health needs of the children involved, identifying and mobilizing services and sources of funds to meet these needs, programming services that build on past health care and patterns for future health care for each child. . . .The planning must be done not for a single child, but for a group of children with diverse needs and patterns of care. Each child must be offered not a standard set of services, but an individual set of services that provides whatever he needs to insure his present and future health."

Additional "problems faced by anyone planning such a program include: what are the health problems to be found in a group of children? What techniques will efficiently identify the children who have each type of problem? What treatment or intervention technique will be most effective in remedying the problems? What financial resources and services are available in the community? How can they be used for Head Start Children? What administrative procedures will be necessary to assure that each child gets whatever services he needs? What can be done to make the future activities of the children and their families more effective in providing and maintaining good health?"

Can we program a computer to solve these problems? Listed in such a way the complexity of the task appears enormous. But there is something familiar about this dissection of Health Care. As the "Winds of Change" blow away the haze, we see revealed The Practice of Medicine! And what computer do we see emerging? Behold! A well-trained, conscientious physician!

We have come full circle.

Walter L. Wilder, M.D.
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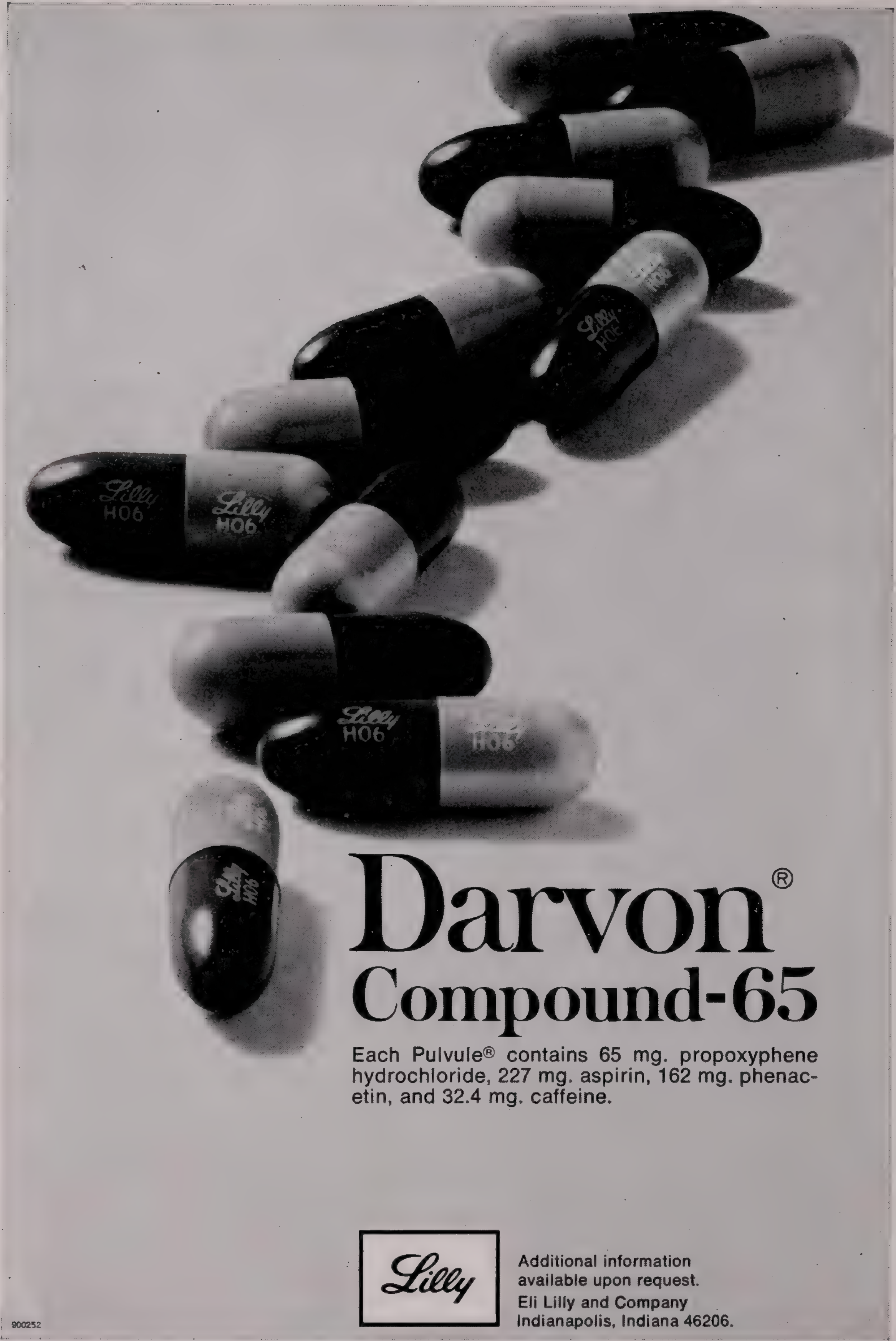

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Anuria Secondary to Ethylene Glycol Intoxication

HENRY T. SMITH, M.D.*
RONALD P. MESSNER, M.D.*
FRED L. SHAPIRO, M.D.*
Minneapolis, Minnesota

ETHYLENE GLYCOL CAUSES an estimated 40 to 60 deaths a year in this country.[1,2] A major cause of death is the associated acute renal failure. The means for salvaging a significant number of these patients are available, if the process is recognized and treated early. The following case report demonstrates that a gratifying response may also be obtained relatively late in the course of the illness with the use of dialysis.

Case Report

History

A 59-year-old white male alcoholic was admitted to a local hospital on October 10, 1967, with a four-day history of anuria. At the time of admission, the patient was confused and markedly dyspneic. There was no history of previous neurological, renal, cardiac or pulmonary disease; nor had there been preceding fever, hematuria or abdominal pain.

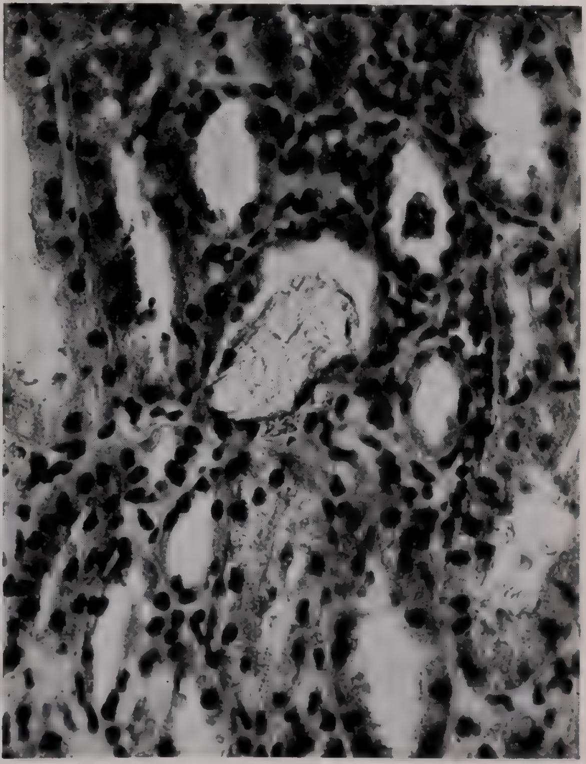

Fig. 1—Calcium oxalate crystal in renal biopsy (×450)

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*Department of Medicine, Hennepin County General Hospital and the University of Minnesota Medical School, Minneapolis.
Reprint requests to 619 S. Fifth St., Minneapolis 55415 (Dr. Smith).

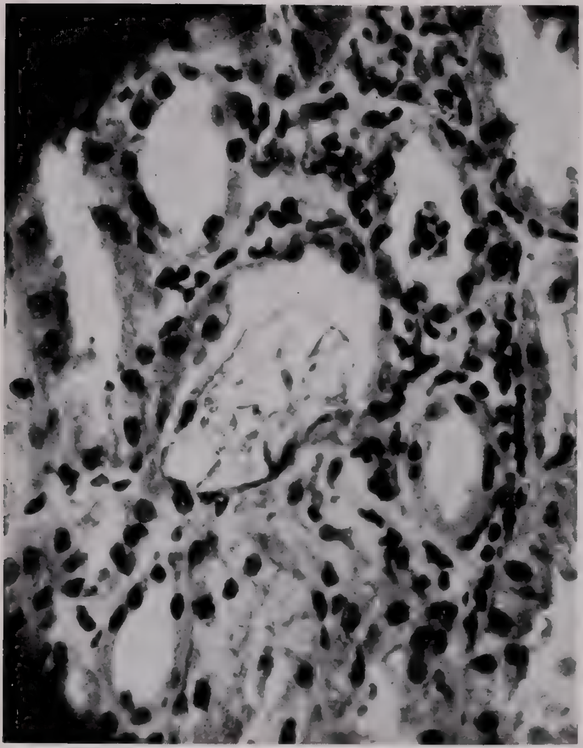


Fig. 2—Same crystal as in Figure 1 with polarized microscopy (×600)

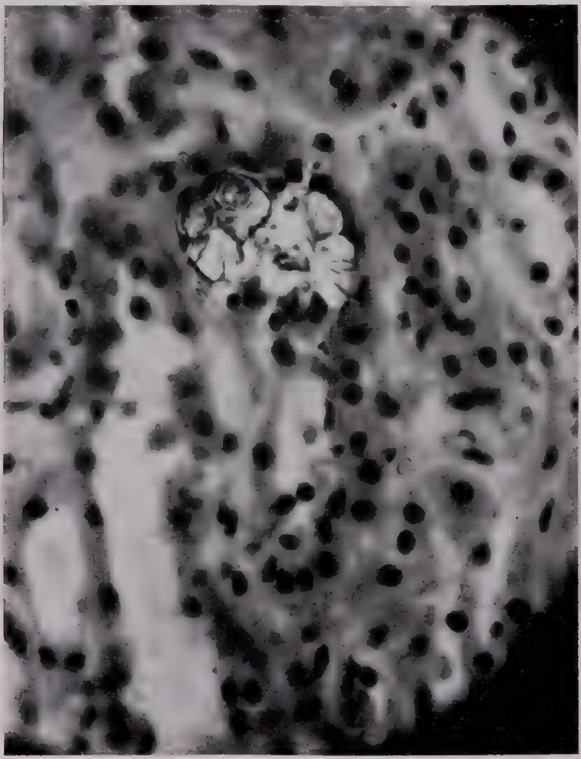


Fig. 3—Calcium oxalate crystal in renal biopsy with polarized microscopy (×600)

Laboratory Studies

Blood urea nitrogen was 81 mg %; serum potassium, 6.1 mEq/L; serum sodium, 124 mEq/L; serum chloride, 92 mEq/L; CO_2, 14 mEq/L; calcium, 9 mg %; creatinine, 15.6 mg %.

A chest x-ray demonstrated cardiomegaly and pulmonary edema.

Treatment and Progress

Peritoneal dialysis was begun immediately and produced gradual alleviation of the patient's respiratory distress. The following day a small amount of urine obtained for analysis revealed 4+ albuminuria; 3+ acetonuria; a specific gravity of 1.011; microscopic—a few bacteria and many red blood cells per high-power field. Cystoscopy and retrograde pyelography showed no evidence of obstruction.

Because the anuria persisted, a kidney biopsy was performed on October 26, 1967. The sections showed a coarse vacuolization in the epithelium of some of the proximal convoluted tubules. In addition, there were sheaves of crystals present in the tubular lumina and epithelium (Figures 1, 2 and 3). The interstitial tissue appeared slightly edematous and contained a few sparsely scattered leucocytes. The glomeruli, vasculature, basement membrane and Bowman's capsule appeared normal. The microscopic diagnosis was chemical nephrosis, probably ethylene glycol. Peritoneal dialysis was continued with four exchanges per day. On the sixth day the dialysate returns became purulent. Antibiotic therapy was initiated with the combination of chloramphenicol 250 mg intramuscularly every six hours, and kanamycin sulfate 250 mg intramuscularly every three days. Culture of the fluid grew out gram-negative rods of the Herella group, which were sensitive to kanamycin sulfate, but resistant to chloramphenicol.

Deterioration Followed by Recovery

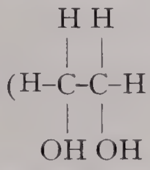
Because of his rapid deterioration, manifested by lethargy, increased confusion, twitching and the development of pericarditis, the patient was transferred to the renal service at Hennepin County General Hospital. At the time of his admission there on November 8, 1967, he was delirious. His blood pressure was 150/90 mm of Hg, pulse rate 120/min and regular, rectal temperature 102.4°F. A loud precordial friction rub was present. There were fine inspiratory rales at both lung bases. The abdomen was distended and diffusely tender; there were no bowel sounds. The admission chest film revealed pulmonary edema. Laboratory data included serum potassium of 5.4 mEq/L, CO_2 28 mEq/L, blood urea nitrogen 81 mg %, SGOT 82 units, and creatinine 12.3 mg %.

Peritoneal dialysis was continued with exchanges on a 1½ hour cycle. There was a nine-pound weight loss over the succeeding 24 hours, but the confusion and cardiac friction rub persisted. Antibiotic therapy was changed to sodium cephalothin 1 gm intramuscularly every six hours and kanamycin 500 mg intramuscularly daily for six days. By November 13, 1967, the patient was afebrile and had normal bowel sounds. It was decided to discontinue peritoneal dialysis and use intermittent hemodialysis as needed. After the patient's mental status improved, he admitted that five days prior to the initial hospitalization, he had ingested approximately three ounces of an unlabeled liquid that he had discovered while painting a relative's home.

By November 15, 1967, the SGOT had increased to 190 units but then decreased (Figure 4). He was discharged from the hospital on December 2, 1967, 59 days post ingestion, and continued the intermittent hemodialysis on an out-patient basis. At the time of discharge, his urine output was 400 cc per day. It had increased to 3300 cc per day by December 20, 1967. He was discharged to the care of his private physician on December 26 with a blood urea nitrogen of 23 mg %, creatinine 1.7 mg %, potassium 5.3 mEq/L and serum glutamic oxaloacetic transaminase of 19 units.

One hemodialysis has been performed since the patient was discharged. He has continued in good health.

Discussion

Ethylene glycol ( $H{-}\underset{OH}{\overset{H}{C}}{-}\underset{OH}{\overset{H}{C}}{-}H$) is widely used as a solvent for dyes and drugs and as a constituent for antifreeze mixtures for automobile cooling systems. It is a nonvolatile, colorless, odorless liquid with a bittersweet taste.[3]

Toxicity

Bachem in 1917 and Page in 1927 drank, respectively, 45 cc and 15 cc of this compound without ill effects, thus emphasizing its nontoxicity.[2] Hunt,[4] however, in 1931, extrapolated from animal experiments that the human lethal dose was approximately 100 cc, an estimate generally borne out by subsequent reports of human fatalities. Fatal doses are quite variable, however, with death reported from ingestion of 60 cc while other patients have survived 240 cc.[3] After ingestion, some of the ethylene glycol is excreted unchanged in the urine in man and animals. Recent evidence suggests that only 3-10% of the amount ingested is converted to oxalic acid.[5,6] The intermediary steps in this process are noted in Figure 5.

Clinical Manifestation

The clinical events following ingestion are usually divided into three stages:[3] (1) central nervous system effects, (2) cardiopulmonary failure and (3) renal damage. Death may occur in any of these stages.

Central nervous system effects are usually noted 30 minutes to 12 hours after ingestion. With relatively small doses the signs may resemble those of ethanol* intoxication. The diag-

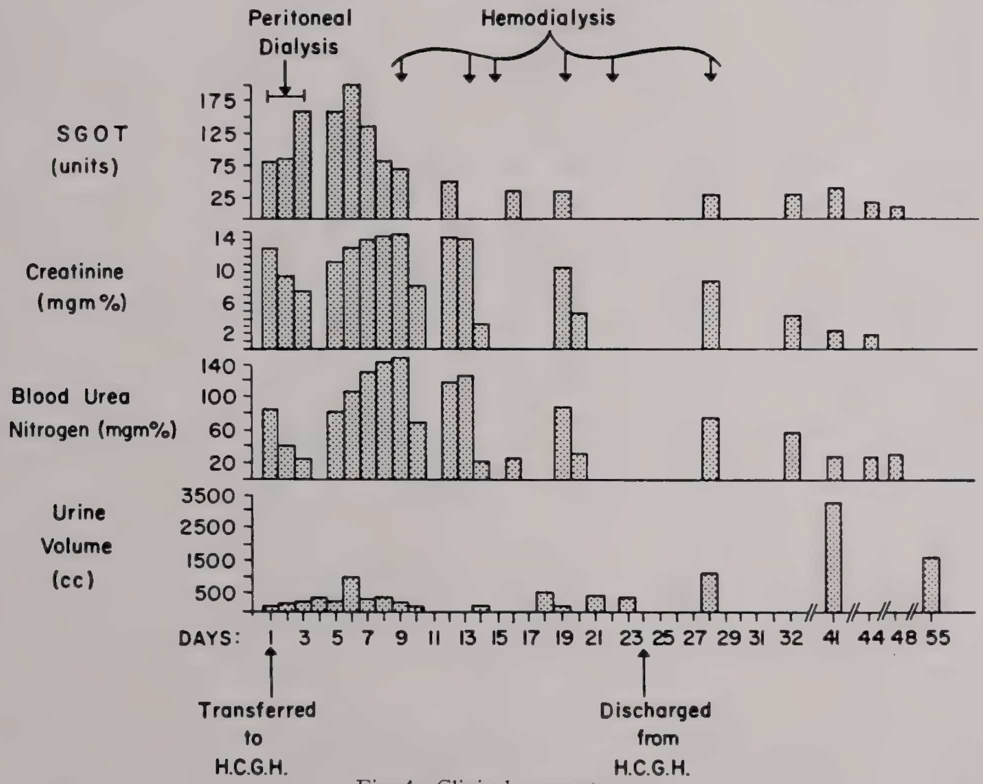


Fig. 4—Clinical parameters

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*See Test Your Word Score Page 1087.

Who Follow A Gleam!

What was its etiology? Was it caused by cold, heat, diet, the moon; by contagion, miasmas (cosmic or telluric), lochial suppression, milk fever (milk pneumonia, milk peritonitis, milk meningitis), gastric biliousness, fibrin deposits culminating in crisis? Or was it intiated by depression, fear, shame, over-crowding, or maybe just rough treatment? This series by no means exhausted the preposterous but quite acceptable hypotheses for the etiology of puerperal fever when Ignaz Philip Semmelweis appeared on the mid-nineteenth medical horizon—to demolish once for all all cart-before-the-horse theories.

Semmelweis' lone and Olympian crusade is familiar to most students of medical history but no less unforgettable now than when Destiny charged him with it.

Voiding space and time we join him in Vienna at the Lying-in Hospital with its two pavilions: Klein's, where the medical students, direct from their autopsy assignments, attended the women patients in labor, and Bartsch's where midwives were trained. Appalling mortality rates prevailed in both pavilions, noticeably higher in Klein's, however, than in Bartsch's. In that puzzling discrepancy lay the key Semmelweis sought: the students, he reasoned, must be conveying something on their hands directly from cadaver to patient. What that something was was invisible, Semmelweis conceded; but since it was not odorless, it could be eliminated by having the students wash their hands until no odor was any longer perceptible.

"Wash hands!" his superiors exploded. "Ridiculous!" Whereupon Semmelweis flew into a rage: a most unseemly exhibition of temper among his smug, complacent colleagues.

"Assassins!" cried Semmelweis. . . . "It is not the maternity hospitals that should be closed to put a stop to the deplorable disasters of which they are the scene, but rather the obstetricians themselves should be driven out, for it is they who behave like real epidemics."

But Semmelweis convinced nobody. True, he had a few friends and supporters; yet when all was said and done, he walked alone, his triumph and vindication delayed until too late.

Had Semmelweis been more patient, more compromising, more diplomatic, the outcome might have been different. But the cooler virtues of patience, compromise, diplomacy do not come natural to revolutionaries; Semmelweis' arsenal contained only the savage fire of his titanic conviction.

A long sequence of scorn, revilement, hostility, ostracism, defeat and dismissal, with the insulting title of "Professor Unattached," shattered the immortal Magyar, culminating in violent and shuddering dementia. One day "he was seen rushing through the streets, pursued by the mob of his imaginary enemies. Howling, he burst into the anatomical amphitheater of the Medical Faculty. A cadaver lay there on the marble, stretched out ready for a demonstration in dissection. Semmelweis seized a scalpel, pushed himself through the circle of medical students, and thus came nearer to the slab. He punctured the skin of the cadaver, shoved the scalpel deep into the putrid tissues before anyone realized what he was doing. He cut the muscles away in strips, hurled them far behind him. . . . Now he took up the scalpel again and explored with his fingers and the blade together a cavity in the dead body which was oozing with liquefaction. With a gesture more abrupt than before, he cut himself profoundly. . . . The wound began to bleed. He shouted. He uttered menaces. He was disarmed at last. But it was too late. . . . As Kolletschka had done years before, he had infected himself fatally." Semmelweis wrote "The Etiology of Puerperal Fever": his grand masterpiece of inductive reasoning and investigation.

With acknowledgements to Louis-Ferdinand Destouches: The Life and Work of Semmelweis, Translated by Robert Allerton Parker, 1937. Also to Frank G. Slaughter, M.D.: Immortal Magyar, 1950.

Vascular Compression of the Distal Duodenum

Clinical Symptoms*

S. K. IMES, M.D.†
Bismarck, North Dakota

VASCULAR COMPRESSION of the distal duodenum is not a new entity. In 1842 Rokitanski[1] first suggested the duodenum might be compressed by the superior mesenteric artery. This syndrome has been described under a number of synonyms, including the superior mesenteric artery syndrome, arteriomesenteric duodenal compression, chronic duodenal stasis, and Wilkie's syndrome.

Literature about this subject well documents the radiologic abnormalities but does not equally well correlate the symptoms with the radiographic findings. This is particularly true with regard to the duodenum in patients treated medically. This paper summarizes the findings in eleven cases of this syndrome and correlates the clinical status with the radiologic findings before and after therapy.

Anatomical Considerations

An excellent and complete resumé of the embryology and gross anatomy of the involved region may be found in the review article of Barner and Sherman.[2]

For the purposes of this paper we reiterate that the third portion of the duodenum lies normally trapped in a potential anatomic pincers‡ the anterior limb of which is formed by the root of the mesentery of the small bowel with its vascular elements. The posterior limb of the pincers is composed of the lumbar spine, the aorta, or the paravertebral muscles. Any mechanism that increases the obliquity of the mesenteric angle closes the pincers and results in compressive occlusion of the distal third of the duodenum.

Fat in the root of the mesentery acts to cushion the third portion of the duodenum from compression; consequently this phenomenon has never been observed in an obese person. Hence, weight loss predisposes to development of the syndrome. The more asthenic the patient, the less weight loss is necessary to produce symptoms.

---

* See editorial page 1079.

†The Department of Radiology, Quain and Ramstad Clinic, Bismarck, North Dakota.

‡See Test Your Word Score Page 1087.

Clinical Picture

Because of the widely varied factors capable of producing this anatomic defect, the age of onset of symptoms varies. In the newborn, congenital anomalies may be the precipitating factor. In the aged patient weight loss and forced bed rest in the supine position may acutely precipitate the syndrome, particularly if the lumbar lordosis is increased by hyperextension of the spine.

We are reporting eleven cases of this syndrome discovered in performing 1,643 upper gastrointestinal radiographic studies on outpatients at the Quain and Ramstad Clinic in a period of 14 months. The youngest of these eleven patients was six years of age and the oldest was twenty-six.

Obstructive Symptoms

The symptoms are due to duodenal distention and partial high small-bowel obstruction. Nausea and/or anorexia are present in nearly all cases. Emesis is also a frequent symptom.

Pain

Pain is a common complaint and is usually epigastric in location, often crampy, occurring soon after meals when semisolids are traversing the duodenum. Pain may occur at night if the supine body position has increased the pincers effect. Many patients will have discovered that curling up on one side or the other, sleeping on the stomach, or assuming the knee-chest position will afford relief, as these positions will open the anatomic pincers. Relief also occurs after vomiting.

The symptoms tend to be chronic, recurrent and episodic. Frequently there are symptom-free periods of days to weeks between attacks. Many patients relate a history of recent weight loss to a recurrence of symptoms. The symptom complex may simulate that of biliary tract disease, peptic ulcer, or pancreatitis. There is evidence that chronic duodenal obstruction probably predisposes to both peptic ulceration and pancreatitis.

X-Ray Findings

Radiologic examination of the upper gastrointestinal tract remains the one reliable method of diagnosis. The initial swallows of barium with the patient erect are likely to show a considerable amount of secretion in the stomach and possibly some gastric dilatation, but with no evidence of outlet gastric obstruction unless there is complicating disease at the pylorus or duodenal bulb. The duodenal bulb will probably be distended. Occasionally antiperistalsis is normally seen to a minimal degree as the first bolus of barium traverses the normal duodenum; but continued or exaggerated reverse peristalsis is not physiologic. In duodenal occlusion, this reverse peristaltic activity is marked and forceful and produces a writhing effect proximal to the obstruction.

Dilatation of the duodenum proximal to the occlusion is always present. Frequently, and especially in long-standing cases, forceful reverse peristalsis distends the duodenal cap and then regurgitates the duodenal contents into the stomach through a patulous* pylorus, the duodenum tending to remain more or less filled up to the point of occlusion. In contrast the normal duodenum is usually only partially filled with the contrast medium. Elongation and redundancy of the duodenum may be present. In the erect right anterior oblique or in the erect lateral fluoroscopic position, the vertical slit-like compression of the distal third portion of the duodenum between the anterior and posterior limbs of the pincers becomes visible.

Even with surging peristaltic activity, the symptomatic patient has no more than small jets of barium pass the level of the compression in the erect position. Barium in small amounts can be forced through the occlusion by increasing the intralumenal pressure proximal to the obstruction by the palpating hand. In the symptomatic patient, the occlusion is usually maintained in the supine position, but can be relieved to a considerable degree in either the left or the right lateral position, the right anterior supine position, or especially in the knee-chest position. For all practical purposes, no other etiology of distal duodenal obstruction will demonstrate this positional relief of the obstruction.

Therapy

Medical

A trial of medical therapy is indicated in nearly all cases. In fact, Bockus[3] has stated that he has never found it necessary to resort to surgical intervention. The success of medical therapy has, however, not been constant in the experience of most physicians. Medical therapy varies according to the severity and the acuteness of the symptoms. The acute episode may require suction tube decompression, intravenous feeding and positional treatment, followed by intermittent ambulation; small, frequent, liquid, high caloric feedings; post-prandial positioning; sleep positioning; and sleeping with the foot of the bed elevated. Antispasmodics and antacids probably have little to offer in the uncomplicated case.

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*See Test Your Word Score Page 1087.

Peptic ulceration or other complications should receive appropriate individual therapy and may in themselves be indications for surgery. Exercises should be instituted to correct abdominal wall muscular deficiencies or lumbar hyperlordosis. Abdominal supports may be useful. Every effort should be made to encourage the underweight patient to gain weight, inasmuch as this factor alone will relieve the symptoms of many patients as a fat pad is added to the mesentery. Diet may be increased and positioning therapy relaxed as the patient gains weight and becomes asymptomatic. The less acute, the chronic and the recurrent patient may be adapted to this regimen at his appropriate level.

Surgery

As early as 1920 Quain[4] reported on the surgical treatment of this abnormality. Surgery should be reserved for those cases where adequate medical therapy fails to relieve the patient's symptoms and produce adequate weight gain and possibly for those cases with complicating ulcer disease or pancreatitis. Barner and Sherman quoted results of surgical therapy as: good, 77%; fair, 13%; poor, 3%; unknown, 2%, and deaths, 4%. Their medical therapeutic statistics list results as good in 50%, fair in 25%, poor in 10%, unknown in 15%. (These figures were corrected for mathematical accuracy.) A valid comparable study of surgical and medical therapeutic results on similar patients is not available.

Case Report Summaries

Table 1 lists the summary of the clinical data related to these eleven patients.

It is noted that clinically all patients presented with cramping, epigastric pain, and nausea. Nine of the eleven patients reported vomiting; eight complained of anorexia. All eleven patients were either quite asthenic in stature or had recently lost significant body weight.

Table 2 summarizes the radiologic findings in these eleven patients.

The radiologic diagnostic abnormalities (gastric retention, proximal duodenal dilatation, duodenal regurgitation, significant reverse duodenal peristalsis and positional relief of the distal duodenal obstruction) were found in all eleven patients.

TABLE I

Clinical Information

Case	Age	Sex	Anorexia	Nausea	Vomiting	Epigastric Pain	Cramping	Height	Weight	Weight Loss Pounds
1.	21	F	++	+++	++	++	++	5′6″	113	8
2.	12	F	++	+++	+++	+++	+++	Asthenic		5
3.	25	M	++	++	+++	+++	+++	5′6″	116	18
4.	6	F		+	++	++	++	Asthenic		5
5.	18	M	+	++	++	++	++	6′1″	140	15
6.	21	F		+		+++	++	5′7″	120	30
7.	20	M	++	++	+++	++++	++++	5′11″	125	5
8.	21	F		+		+++	++	5′6″	117	30
9.	18	M	++	+++	++	+++	+++	6′4″	170	8
10.	16	M	++	++	+	++	++	6′0″	140	30
11.	26	F	+++	+++	+	+++	+++	5′5″	116	65

Follow-up Studies

The status of these eleven patients following therapy is listed in Table 3.

Excellent correlation is demonstrated between the degree of weight gain, the relief of symptoms, and the radiologic demonstration of relief of distal duodenal obstruction.

Case Reports

Four cases were of special interest because of certain facets of their histories, findings, and delayed studies.

Case 1

A 21-year-old lady who had intentionally lost eight

TABLE 2

Radiologic Findings

Case	Gastric Fluid	Proximal Duodenal Dilatation	Duodenal Regurgitation	Reverse Peristalsis	Distal Duodenal Obstruction	Positional Relief of Obstruction
1.	++	+++	+++	+++	+++	Yes
2.	+++	++++	+++	+++	+++	Yes
3.	++++	++++	++++	+++	+++	Yes
4.	+	++	++	++	++	Yes
5.	++++	+++	++++	++++	++++	Yes
6.	+	+++	+	+++	+++	Yes
7.	+++	++++	++++	++++	++++	Yes
8.	++	+++	+++	+++	+++	Yes
9.	+++	++++	+++	++++	+++	Yes
10.	+++	++++	++	+++	+++	Yes
11.	+++	++++	+++	+++	+++	Yes

TABLE 3

Follow-up Studies

Case	Pre-Rx Pounds Wt. Loss	Post-Rx Pounds Wt. Gain	Therapy	Follow-up Period	Clinical Status	Radiologic Status
1.	8	None	Medical	1 year	Episodic recurrence of symptoms.	Unchanged
2.	5	10	Medical	1 year	Symptom-free in two months.	Normal
3.	18	14	Medical	8 months	Symptom-free in two months.	?
4.	5	8	Medical	1½ years	Symptom-free in three months.	?
5.	15	10	Medical	8 months	Moderate relief only. Follows regimen poorly.	?
6.	30	13	Medical	7 months	Symptom-free in one month.	Mild residual duodenal dilatation. No obstruction.
7.	5	30	Medical Surgical	1½ years	Recurrent pancreatitis.	Gastrojejunostomy. Residual duodenal loop stasis.
8.	30	0– 18	None Medical	6 months 1 year	Unimproved Symptom-free in two months.	Unchanged Normal
9.	8	8	Medical	5 months	Symptom-free in three months.	Normal
10.	30	10	Medical	6 months	Episodic recurrence of symptoms. Relief with diet and positioning.	Retains + x-ray findings, but to a lesser degree.
11.	65	10	Medical	1 year	Symptom-free in one month.	Normal

pounds to more nearly attain a "Twiggy-look." She learned to control her episodic symptoms with diet, after-meal positioning and sleep positioning when symptoms occurred, and had no intention of adding weight.

Case 8

A lady who had lost 30 pounds and had moderately severe symptoms with radiologic findings of distal duodenal obstruction. Through lack of communication between the Radiology Department and the clinician, this lady received no treatment. At the end of six months her symptoms and radiographic findings were identical with those at the initial study. She was then placed on a moderately strict medical regimen; and, three months later with a weight gain of 18 pounds, she was asymptomatic and an upper gastrointestinal radiologic study was normal.

Case 11

A 26-year-old lady who had been considerably overweight since childhood. By dieting she gradually reduced her weight from approximately 180 to 130 pounds and at this weight level presented with abdominal discomfort of recurrent and indefinite nature. An upper gastrointestinal radiologic study at that time appeared normal. During the next nine months she unintentionally reduced to 116 pounds; at this weight she returned with characteristic symptoms of vascular duodenal compression. A re-check upper gastrointestinal series demonstrated class and marked findings of vascular compression of the distal duodenum. She was placed on a medical regimen with frequent high caloric feedings and post-prandial positioning. Within one month she had regained ten pounds, was symptom-free, and has remained so at this weight for a period of twelve months.

Case 7

Of considerable interest was the one complete failure of medical therapy: a young man who has always been asthenic in stature. He was 5 feet, 11 inches tall and weighed 116 pounds. For as long as he could remember he had always had recurrent crampy post-prandial upper abdominal pain, with severe disabling episodes associated with vomiting lasting for periods of up to a week. Three years before our first radiographic examination he was thought to have had a superficial duodenal ulcer on gastrointestinal x-ray studies done elsewhere. Vagotomy and pyloroplasty were performed at that time, and he was discharged with an associated clinical diagnosis of pancreatitis based on a transient elevation of serum amylase during hospitalization. Despite this, his symptoms remained unchanged.

Our upper gastrointestinal series three years later demonstrated severe vascular duodenal compression of the distal duodenum; and review of the original radiographs revealed that the earlier obstruction had been equally severe. The patient was hospitalized and placed on a rigid medical regimen with only temporary and partial relief of symptoms. Within a month, in spite of careful adherence to the medical regimen, he had to be re-hospitalized, and a gastrojejunostomy was done. Postoperatively he has remained free of duodenal obstructive symptoms for a period of well over twelve months; but unfortunately he has had recurrent episodes of pancreatitis with increasing frequency and severity in spite of careful medical management. Recently he has had a duodenojejunostomy performed to provide better drainage of the duodenal loop inasmuch as his re-check upper gastrointestinal x-rays have repeatedly demonstrated considerable stasis in the duodenal loop and continued regurgitation of duodenal contents into the stomach. At the recent surgery, the common bile duct was explored and found to be stenotic at its distal end. A sphincterotomy was then done. Significant time has not elapsed, however, to evaluate the clinical effects of the latest procedures on the pancreatitis.

Summary

Vascular compressive disease of the distal duodenum can produce nausea, vomiting and pain—typical symptoms of duodenal obstruction. X-ray studies confirm the diagnosis. Asthenic body stature and recent weight loss are felt to have been most important to the development of symptomatology in all of these cases. Radiologic studies at the time of diagnosis and repeat studies on eight cases following therapy demonstrate close correlation of clinical symptomatology and radiologic findings.

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Dream, yes. But, also, wake up!—Forbes Epigrams

I am indebted to the Bismarck Medical Foundation for a grant of funds for the follow-up studies of these patients.

Old Hospitals

Hospital de Jesús Nazareno, Mexico City.

Oldest Hospital in the Americas.

Pictured is a courtyard of the Hospital de Jesús Nazareno in Mexico City. Founded in 1523 by Hernando Cortés, the conqueror of Mexico, it is the oldest hospital in the western hemisphere. In a conference room, frequently used by Cortés himself, hangs the only portrait of the founder ever done in life. Cortés' remains are in the church connected to the hospital.

The original building is still in use, housing the surgical suite, administration and business offices, and the kitchen. In 1942, the old building was surrounded by a modern hospital and medical office building. It is located about three blocks south of the Zócalo or main square of the city, within easy reach of visitors. The hospital has developed its own plan to provide hospitalization for persons not covered by Mexican Social Security.

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The Concept of Disease

The term disease is a concept we form by study of like illness in different persons and a concept can produce no symptoms. It cannot be wholesome that the body of medical writing and thought should be characterized by so erratic a use of our working symbols.*

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*Walshe, F. M. R. in Richard Magraw: Ferment in Medicine, 1966.

Everything that exceeds the bounds of moderation, has an unstable foundation.—Seneca

Congenital Pseudarthrosis of the Ulna

Report of Two Cases

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CONGENITAL PSEUDARTHROSIS of long bones in children is uncommon, although, when present, it most frequently involves the tibia. There are rare reported cases of this congenital anomaly affecting other long bones, including the fibula, femur, clavicle, humerus, first rib, and ulna. A review of the English literature reveals two cases of congenital pseudarthrosis of the ulna.[1-3] The two patients whose cases are presented in this paper were treated by several orthopedists and their treatment represents different approaches to the management of this uncommon problem.

The therapeutic objectives of treating congenital pseudarthrosis of the ulna are primarily to maintain good function of the hand and secondarily to prevent or decrease deformity and maintain length of the forearm.

In the first case, the distal ulna was excised and the distal radius osteotomized. In the second case, three bone-grafting procedures were required to effect union of the ulna and maintain functional alignment of the hand on the forearm. Both patients have had sufficiently long follow-up periods to allow final appraisal of the therapeutic program employed.

Report of Cases

Case 1

This five-year-old boy was first seen in September 1956. The chief complaint was mild lateral bowing of the left forearm. There was no history of trauma, pain, or disability related to the deformity. At the original orthopedic examination, the patient was noted to have many café-au-lait§ spots widely distributed on his trunk. Roentgenographic examinations of the left forearm when the patient was one year old, three years old, and five years old (1956) revealed congenital pseudarthrosis of the left ulna (Figure 1 A). Since there was minimal disability it was elected to observe the child for increasing disability or deformity. The boy was examined periodically, and in 1961 the lateral bowing of the left forearm was noted to have increased significantly (Figure 1 B).

First Operation

In July 1961, when he was 10 years old, the distal ulna consisting "mostly of white fibrocartilage" was excised and a wedge of the distal radius removed, thus placing the hand in a better functional position. The osteotomy site appeared to heal satisfactorily, but one year later the boy injured his left forearm and a roentgenographic examination revealed a fracture through the osteotomy site.

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§See Test Your Word Score Page 1087.

Second Operation

In June 1962, a second operation consisting of bone grafting across the fracture site was done, using iliac bone and Kirschner-wire fixation. This procedure produced a solid union (Figure 1 C), and in six months the patient was permitted to engage in normal activities, with the exception of body-contact sports.

The boy was seen most recently in September 1967, when he was 16 years old, seven years after the distal portion of the ulna had been excised. Clinically, there was minimal bowing deformity, but obvious shortening of the left forearm was present (Figure 1 D). Hand function was good, although forearm motion was impaired.

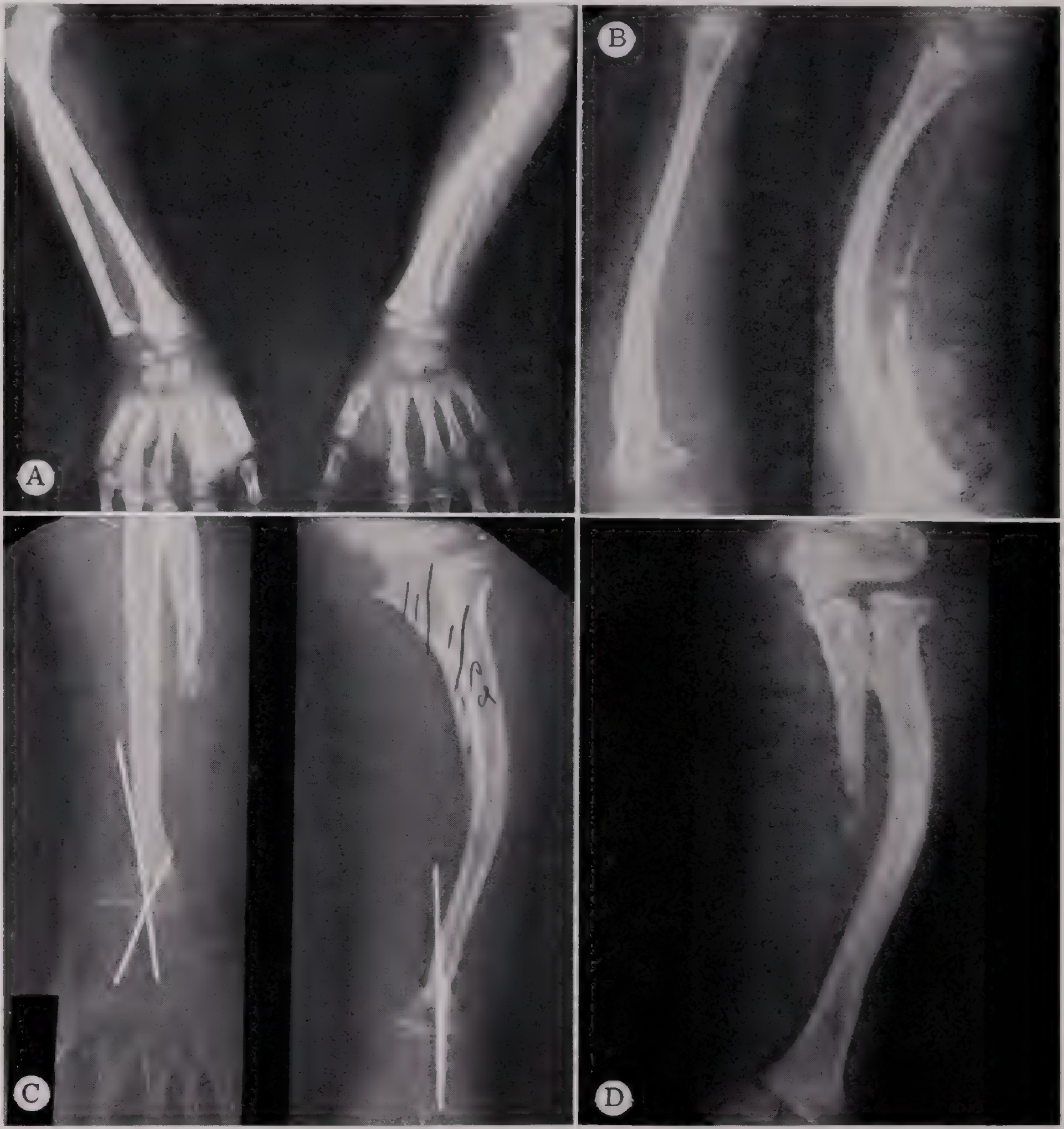

Fig. 1—(Case 1). (A), Patient at five years (1956). Both forearms showing congenital pseudarthrosis of left ulna, with mild shortening and lateral bowing of left radius. (B), July 1961. Bowing of left radius has increased significantly, and the thin atrophic ulna appears to be producing a bowstring effect. (C), November 1962. Five months after second operative procedure on left forearm. Distal radial osteotomy appears united. (D), Patient at 16 years (1967). Left forearm six years after resection of distal ulna for congenital pseudarthrosis. Lateral bowing of radius has persisted and increased slightly.

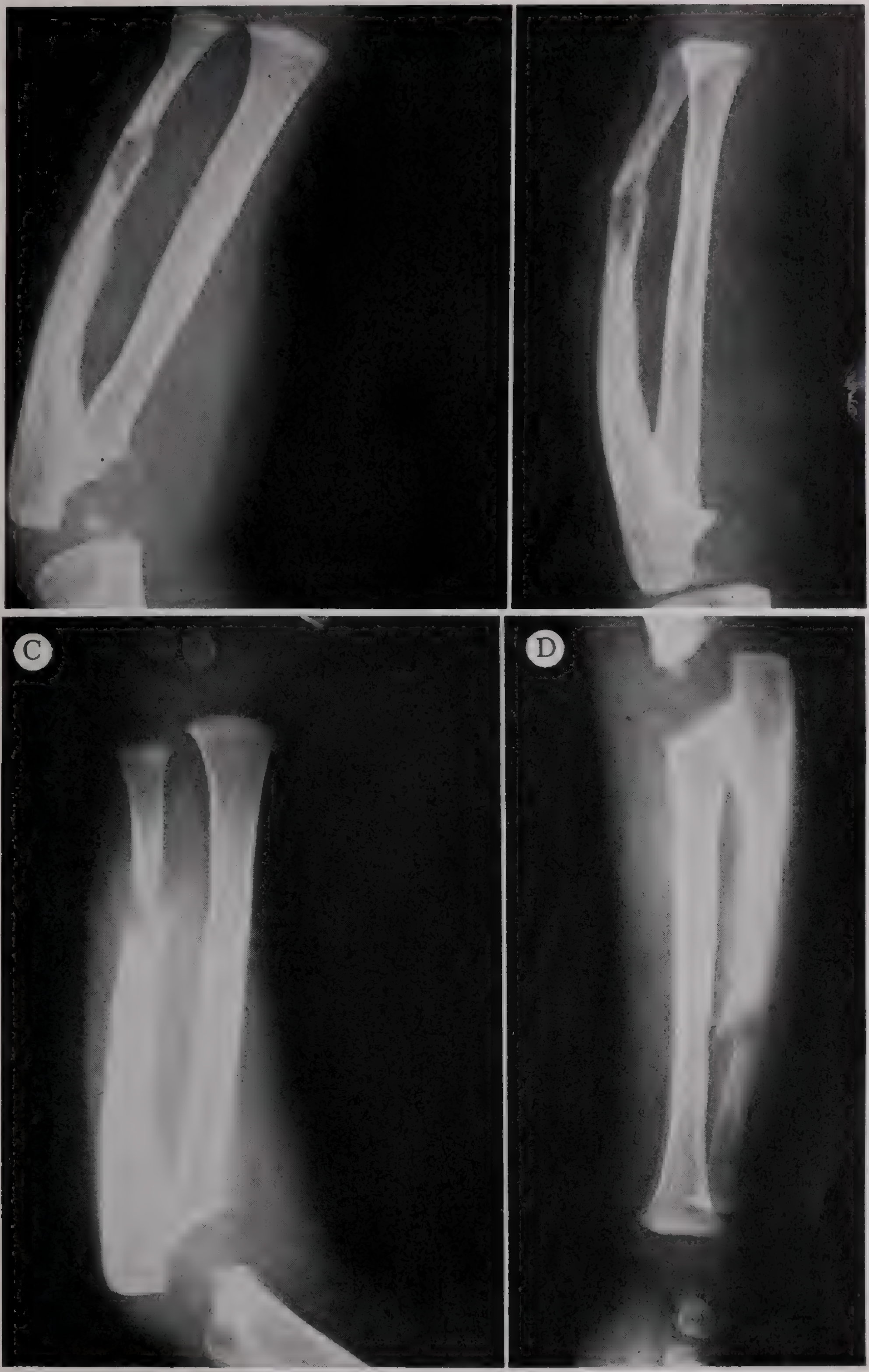

Fig. 2—(Case 2). (A) and (B) (top) Patient at 13 months (January 1955). Left forearm shows cystic lesion in ulna. There is also an irregularity of proximal ulnar cortex and an abnormal conformation of left radius. (C) and (D), May 1955. Left forearm after four months of long arm cast immobilization. Obvious pseudarthrosis with mild shortening of ulna and mild bowing of radius. Apparent periosteal reaction of radius and ulna is an artifact owing to motion when roentgenogram was taken.

Case 2

This patient was seen when she was 13 months old in January 1955 because her mother had noticed swelling on the proximal end of the ulnar side of the left forearm. The child had no noticeable discomfort when she used her left upper extremity, which she did normally. There was no history of trauma to the child or a similar deformity in the family. The child had 20 to 30 brown pigmented lesions on her face and trunk, which were present at birth and were described as café-au-lait spots. Roentgenograms of the left forearm showed a "cyst in the left ulna, with a pathologic fracture" (Figures 2 A and B).

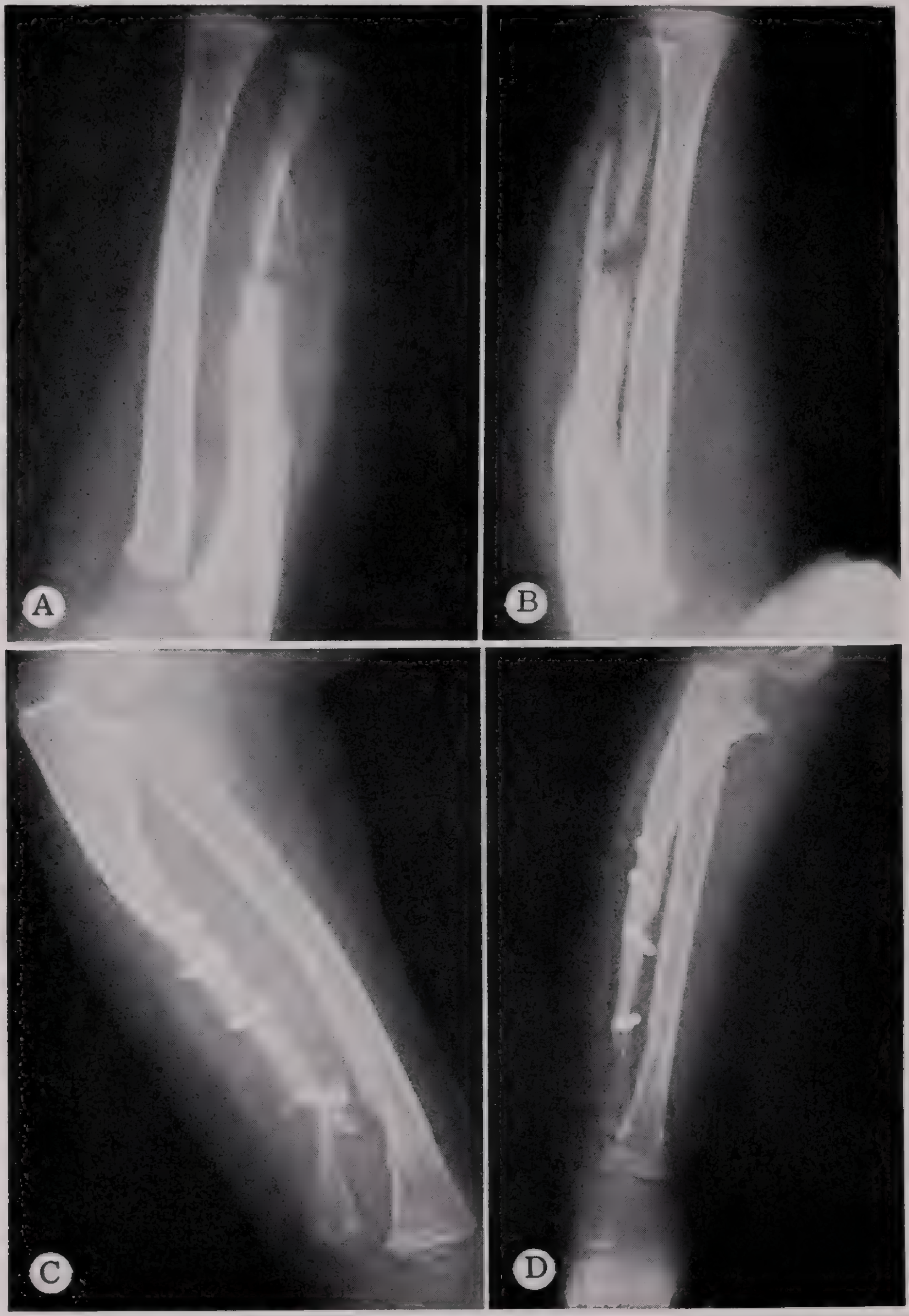

Fig. 3—(Case 2). (A) and (B), July 1955. Tibial bone graft to left ulna six months after operation. Graft failed to unite to either the proximal or distal ulna. (C) and (D), April 1957. Four months after second tibial bone grafting procedure for congenital pseudarthrosis of ulna. Grafts appeared united to the proximal ulna but bone has resorbed at lower end of graft, with fracture and angulation of distal ulna.

First Operation

The patient was referred to an orthopedist* who initiated treatment by immobilizing the left forearm in a cast for four months. When the cast was removed, there was no evidence of union (Figures 2 C and D), and in May 1955 a grafting procedure with autogenous tibial bone was performed on the left ulna. The pathologic diagnosis of a biopsy specimen from the site of pseudarthrosis was reported to be an "ossifying fibroma."

Postoperatively the arm was immobilized in a long arm cast for six months. After the cast was removed, the child continued to have a painless pseudarthrosis (Figure 3 A and B), minimal deformity, and no disability. For a year after the cast removal, she used the arm normally, being able to "chin" herself with no discomfort. During this time the lateral bowing of the forearm and medial displacement of the wrist became more noticeable. In November 1956 a roentgenogram revealed an eroded area on the cortex of the distal end of the left radius.

The patient was referred to the Mayo Clinic in January 1957. In addition to the café-au-lait spots noted before, she also had a hemangioma on the abdominal wall. Laboratory data, including values for serum calcium, phosphate, and alkaline phosphatase, were normal. Results of funduscopic examination were normal.

Second Operation

On January 22, 1957, the fibrous pseudarthrosis was resected; a single autogenous tibial onlay graft and homogenous iliac bone grafts were applied to the left ulna; and fixation was obtained with special small stainless-steel screws. A biopsy specimen of the cortical erosion of the radius revealed noninflammatory fibrous tissue, and a specimen of the pseudarthrosis site showed fibrous tissue with foci of new bone formation. Postoperatively the patient was placed in a modified shoulder spica.

After four months of immobilization, roentgenograms revealed that the grafts had united at the proximal end of the pseudarthrosis but that bone had been resorbed at the lower end of the graft, with fracture and angulation of the distal end of the ulna (Figures 3 C and D).

Third Operation

Another grafting procedure with a single onlay of autogenous tibial bone was performed on April 30, 1957, four days after the cast was removed following the second operation. The patient was again immobilized in a shoulder spica for three months, after which the arm was immobilized in a long arm cast for six months. Roentgenograms at the time immobilization was discontinued showed satisfactory union, although thinning of the distal ulna was worrisome. The forearm was protected with a leather-lacer cuff for an additional year. The screws were removed in March 1960.

The patient was examined in July 1966, at which time she had minimal clinical and roentgenographic deformity, a one-inch shortening of the left upper extremity, and a full range of motion of the hand, wrist, and elbow (Figure 4).

Discussion

Each of the two cases presented seems to be different from the other and from the two reported previously in the literature. Describing the technique of delayed autogenous bone grafting for surgical correction of congenital pseudarthrosis, J. R. Moore,[3] in 1949, presented a series of eight patients, one of whom had congenital pseudarthrosis of the ulna. The anomaly was long-standing, with obvious deformity noted at birth. In addition to pseudarthrosis of the ulna, the distal ulna was atrophic and the radial head was dislocated.

In 1956 Madsen[1] reported a boy with congenital pseudarthrosis who was first seen by an orthopedist at the age of six years. The forearm deformity had been noted when the boy was two years old. Because of associated congenital deformities, including neurofibromatosis, kyphoscoliosis, spina bifida, and mental retardation, treatment was postponed. When the boy was 10 years old, the bowing of the forearm was increased significantly and the radial head was dislocated. It is interesting to speculate whether, had the deformity been allowed to progress in the two cases presented here, it

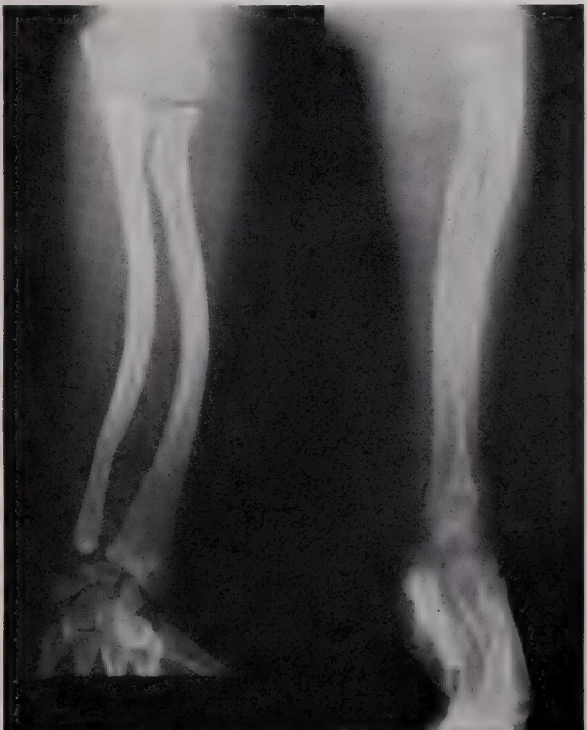

Fig. 4—(Case 2). Patient at 12 years (July 1966). Nine years after third bone grafting procedure of left ulna. There is solid union, with a poorly developed medullary canal.

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*The initial history, physical examination, x-rays, and first operative report as well as progress reports and x-rays for Case 2 were supplied by Dr. Robert F. Kimbrough, Fort Wayne, Indiana.

too would have eventually dislocated the radial head, resulting in limitation of elbow and forearm motion.

Case 2 illustrates many of the problems seen in congenital pseudarthrosis of the tibia. Adequate immobilization failed to produce union. The first bone graft "melted" away, as is frequently seen when congenital pseudarthrosis of the tibia is treated. The second grafting procedure resulted in a union of the graft to the proximal end of the ulna, but a gradual thinning and fracture of the ulna at the distal end of the graft necessitated a third operation. Even after the third tibial bone grafts united, the surgeon suggested the need for restricted mobility of the extremity and anticipated the delayed development of an intramedullary canal.

Neurofibromatosis

Both of our patients had numerous café-au-lait spots, and one patient (Case 2) had a subperiosteal cyst. Both of these findings have more than a casual relationship with neurofibromatosis. Of the eight patients with congenital pseudarthrosis in Moore's series,[3] seven had café-au-lait spots. In 1950, McCarroll[2] reported the clinical manifestations of 46 patients with congenital neurofibromatosis. Thirty-three of these patients and all of the five patients with congenital pseudarthrosis of the tibia in McCarroll's series had café-au-lait spots. Some investigators[4] believe that café-au-lait spots are diagnostic of neurofibromatosis. Such spots, however, are frequently found in normal people who have no family history or clinical manifestations of neurofibromatosis.

The pathologic diagnosis of the tissue taken from the site of the pseudarthrosis was reported to be "fibrous tissue with foci of new bone formation" in Case 2.

Summary

Two cases of congenital pseudarthrosis of the ulna have been presented. One patient was treated by resection of the short, atrophic distal end of the ulna, which the surgeon believed was acting as a bowstring, resulting in lateral bowing of the forearm and in ulnar drift of the hand. The other patient was treated by bone grafting to obtain solid union at the site of pseudarthrosis.

Early diagnosis and treatment of congenital pseudarthrosis of the ulna may avoid the complication of dislocation of the radial head and will preserve good function of the hand by maintaining satisfactory radial carpal alignment.

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School of Salernum

The Priests rule is (a Priests rule should be true)
Those Egges are best, are long, and white and new.
Remember eating new laid Egges and soft,
For every Egge you eat you drink as oft.
—Regimen Sanitatis Salerni

Editor's note: Most delicious here is the jibe at clerical infallibility. Some people might prefer round, brown eggs, but who would care to violate the clergy's injunction that long white eggs are preferable. As for quaffing (water? wine?) each time you consume a soft-boiled egg, was the School serious or did it have its tongue in cheek?

Antibiotic Therapy and Hospital-Acquired Infections*

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INFECTIONS IN HOSPITALIZED patients continue to be a serious problem, especially on surgical services. This is in part due to the increased application of major surgical procedures in poor-risk patients and medical management with immunosuppressive measures. The reckless use of antimicrobial therapy may also be implicated.[1,2] The spectrum of microorganisms associated with hospital-acquired infections is changing. Endogenous gram-negative bacteria, often demonstrating multiple antibiotic resistance, are now more frequently associated with hospital-acquired infections than previously.[1,4]

This report describes problems with infections on the surgical services of the University of Minnesota Hospital during a six-month period (January 1, 1967 through June 30, 1967). The types of microorganisms most frequently associated with hospital-acquired infections were correlated with certain aspects of antibiotic therapy.

Methods

Six hospital stations with a total of 147 beds were included in this infection survey: four general surgery stations, one orthopedic and one surgical intensive care unit.

During the period of the study all patients considered to have an infection were reported to one of us (A.A.L.) by the station Nurse-In-Charge. Suggestions were made to patients' responsible physicians regarding isolation procedures and the patients were followed until discharge from the hospital. At the completion of the infection survey the hospital charts of all patients considered to have infections during this period were reviewed, and those considered

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See editorial page 1081.

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to have infections defined as "hospital-acquired infections"[5] were included in this report. Urinary tract infections included symptomatic patients with greater than 50,000 bacterial colonies per ml of urine and asymptomatic patients with urinary bacterial colony counts greater than 100,000 colonies per ml.

Results

Infections were diagnosed in 135 patients on the six hospital stations during the period of this study. Of these 135 patients there were 95 with infections defined as "hospital-acquired." Since there were 1,850 patients admitted to these stations during this period, the hospital-acquired infection rate was 5.2%

Wound Infections

The types of hospital-acquired infection included in this analysis are shown in Table 1. As would be expected, since this is a review of surgical services, the most frequent hospital-acquired infections were wound infections. There were 42 patients with two or more infections; therefore the total number of hospital-acquired infections (149) is greater than the number of patients with infections (95).

TABLE 1

Hospital-Acquired Infections.

Type	Number and Percentage
Wound	67 (45.0%)
Superficial, not postoperative	8 (5.4%)
Septicemia	20 (13.4%)
Peritoneum and biliary	4 (2.7%)
Respiratory tract	32 (21.5%)
Urinary	18 (12.1%)
Total	149 (100%)

The Organisms

There were 20 species of microorganisms

TABLE 2

Bacteria Associated with Hospital-Acquired Infections.

	Wound	Superficial	Respiratory	Septicemia	Urinary Tract	Peritoneum and Biliary	Total
Staph. aureus	22	2	7	5			36 (14.8)
Strep., not β-hem.	11		13	2	4	3	33 (13.5)
Staph. epidermidis	18		4	3			25 (10.3)
E. coli	14		4		5		23 (9.4)
Pseudomonas	6		8	7	1		23 (9.4)
Klebsiella	4		5	4	8	1	21 (8.6)
Proteus	55		3	3	5		16 (6.6)
Enterobacter	8		2	2	1	1	14 (5.7)
Neisseria	1		12				13 (5.3)
Diphtheroid	2	1	3	2			8 (3.3)
Hemophilus			6				6 (2.5)
Pneumococci			6				6 (2.5)
Clostridium	3		1	1			5 (2.1)
Strep., β-hem.	2		2		1		5 (2.1)
Herellea	4						4 (1.6)
Citrobacter	1				1		2 (0.8)
Serratia	1						1 (0.4)
Bacterioides	1						1 (0.4)
Bacillus sp.				1			1 (0.4)
C. albicans					1		1 (0.4)
Total	103	3	76	30	27	5	244 (100)

*Numbers represent number of isolations.

TABLE 3

Bacterial Etiology of Hospital-Acquired Infections and Antibiotic Therapy.

Organisms	Group I No Antibiotics	Group II Penicillin and Semi-Synthetic Penicillin	Group III Broad-Spectrum Antibiotics and Ampicillin*
Gram-positive cocci†	50	8	47
Enteric bacilli‡	20	14	68
Miscellaneous#	12	6	19
Total	82	28	134

*Any broad-spectrum antibiotic or antibiotics aimed at gram-negative bacteria, alone or in combination with any type of antibiotic.

†Staphylococci, streptococci and pneumococci.

‡E. coli, Enterobacter, Pseudomonas, Proteus, Klebsiella, Herellea and Serratia.

#Hemophilus, Neisseria, diphtheroids, Bacterioides, bacillus species and Candida.

TABLE 4

Hospital-Acquired Septicemia.

Patient	Organisms Isolated	Antibiotics Given Before Culture	Trauma or Operation	Survival
A.E.	Staph. coag+	None	Intra-abdominal	Yes
M.M.	Staph. coag+ Strep Clostridium perf.	None	Severe burns	No
E.N.	Staph. coag+	None	Open-heart	No
J.M.	Diphtheroid	None	Open-heart	Yes
L.K.	Staph. coag.-*	Penicillins	Kidney transplant	Yes
R.B.	Klebsiella	Penicillins	Intra-abdominal	No
R.H.	Enterobacter	Penicillins	Open-heart	Yes
C.G.	Staph. coag.- Bacillus sp.	Penicillins	Kidney transplant	No
C.M.	Pseudomonas	Broad spectrum	Intra-abdominal	No
W.H.	Staph. coag+ Pseudomonas Proteus	Broad spectrum	Kidney transplant	No
L.K.	Pseudomonas*	Broad spectrum	Kidney transplant	Yes
L.D.	Staph. coag.-*	Broad spectrum	Open-heart	No
D.W.	Pseudomonas Strep	Broad spectrum	Kidney transplant	No
M.R.	Staph. coag+ Pseudomonas	Broad spectrum	Kidney transplant	Yes
W.B.	Pseudomonas Diphtheroid Proteus	Broad spectrum	Intra-abdominal	No
V.B.	Klebsiella	Broad spectrum	Cancer, pelvic	No
O.K.	Pseudomonas	Broad spectrum	Cancer, mouth	No
B.H.	Klebsiella	Broad spectrum	Intra-abdominal	No
R.E.	Enterobacter	Broad spectrum	Open-heart	No
T.S.	Klebsiella Proteus	Broad spectrum	Cancer, penis	No

*Same patient.

associated with hospital-acquired infections (Table 2). It is noted that *Staphylococcus aureus* accounted for more infections (14.8%) than any other single species; however, the enteric gram-negative organisms *E. coli, Pseudomonas, Klebsiella, Proteus* and *Enterobacter* accounted for 39.7% of the hospital-acquired infections. Not included in this analysis were 10 patients with inflammatory lesions which were not cultured and six patients with purulent wound drainage but no growth on culture.

The Antibiotic

The bacterial etiology of infections in these patients was analyzed in regard to the antibiotics they were receiving at the time signs and symptoms of infection developed (Table 3). The patients were divided into groups as follows: Group I—no antibiotics; Group II—penicillin G or semi-synthetic penicillins; Group III—broad spectrum antibiotics (including ampicillin) and combinations of antibiotics. Infections included in Group II and Group III are those in which the culture was taken at least 24 hours after the antibiotic had been started for prophylaxis or treatment of other infections. It is noted that 47% of the patients with gram-positive cocci were receiving broad-spectrum antibiotics and 50% were not receiving antibiotics. Sixty-eight percent of patients with gram-negative bacterial infections were receiving broad-spectrum antibiotics.

Septicemia

There were 19 patients on these surgical services who developed septicemia during the study period (Table 4). Four of the patients with septicemia were not receiving antibiotics when the septicemia was diagnosed, four were receiving penicillin and eleven were receiving broad-spectrum antibiotics. All of seven patients with Pseudomonas septicemia were receiving broad-spectrum antibiotics.

There were 148 patients on whom open-heart operations were done during this period; five of these patients developed sepsis (3.4%). A single bacterial species was recovered from the blood in all of these patients. There were eight patients who received a renal transplant during this study period. Five of these developed sepsis (62.5%). In contrast to the experience with open-heart surgery patients, all of the patients with transplanted kidneys who developed sepsis demonstrated more than one species of bacteria in their blood. One patient had two separate episodes of septicemia, each due to a different type of bacteria (Table 4).

Septicemia with multiple bacterial species also occurred in one patient with a severe burn and in another with multiple internal and external fistulae following traumatic tear of the common bile duct.

Discussion

The problems of hospital-acquired infections in patients continue to be seemingly insoluble in our present state of ignorance. This study confirms observations of others that enteric* bacilli and staphylococci are the major types of bacteria involved in hospital-acquired infections.[1-4,6,7] The rate of infection (5.2%) is in general similar to reports from other university hospitals.[3,4]

The majority of the patients were receiving antimicrobial therapy when bacteriologic evidence for infection was revealed. Other studies have also directed attention to the failure of antimicrobial therapy to prevent infections.[3,4,6,7,8,9]

The observations on antimicrobial therapy in patients with infections and especially with septicemia are clear evidence that infection with certain bacteria occurs and persists despite antibiotics. Strains of *Pseudomonas* and the *Klebsiella-Enterobacter* group were recovered from 13 of the 19 patients with septicemia. All of these patients were receiving antibiotics for at least 24 hours before diagnosis of sepsis. Indeed 11 of the 13 were receiving broad-spectrum coverage. A similar, but less dramatic correlation, was noted in all types of hospital-acquired infections.

These observations do not allow a definite conclusion that antibiotics predispose to hospital-acquired infections since we have no data on non-infected patients. It is obvious, however, that antimicrobial therapy does permit serious infections with opportunistic organisms in susceptible patients.

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*See Test Your Word Score Page 1087.
References may be secured from the author.

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Indication—Oral contraception.

Contraindications—Thrombophlebitis, thromboembolic disorders, cerebral apoplexy or a past history of these conditions, markedly impaired liver function, known or suspected carcinoma of the breast, known or suspected estrogen-dependent neoplasia, undiagnosed abnormal genital bleeding.

Warnings—Watch for the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, retinal thrombosis); if present or suspected discontinue the drug immediately.

British studies reported in April 1968[1,2] estimate there is a seven- to tenfold increase in mortality and morbidity due to thromboembolic diseases in women taking oral contraceptives. In these controlled retrospective studies, involving 36 reported deaths and 58 hospitalizations due to "idiopathic" thromboembolism, statistical evaluation indicated that the differences observed between users and non-users were highly significant. The conclusions reached in the studies are summarized in the table below:

Comparison of Mortality and Hospitalization Rates Due to Thromboembolic Disease in Users and Non-Users of Oral Contraceptives in Britain.

Category	Mortality Rates		Hospitalization Rates (Morbidity)
	Age 20-34	Age 35-44	Age 20-44
Users of Oral Contraceptives	1.5/100,000	3.9/100,000	47/100,000
Non-Users	0.2/100,000	0.5/100,000	5/100,000

No comparable studies are yet available in the United States. The British data, especially as they indicate the magnitude of the increased risk to the individual patient, cannot be applied directly to women in other countries in which the incidences of spontaneously occurring thromboembolic disease may differ.

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or sudden onset of proptosis, diplopia or migraine. Withdraw medication if papilledema or retinal vascular lesions are found.

Since the safety of Ovulen in pregnancy has not been demonstrated, it is recommended that pregnancy be ruled out for any patient who has missed two consecutive periods before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule the possibility of pregnancy should be considered at the first missed period.

A small fraction of the hormone agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect on the nursing infant cannot be determined at this time.

Precautions—Pretreatment physical examination should include special reference to the breasts and pelvic organs, and a Papanicolaou smear.

Endocrine and possibly liver function tests may be affected by Ovulen. Therefore, it is recommended that such tests if abnormal be repeated after the drug has been withdrawn for two months.

Pre-existing uterine fibromyomas may increase in size under the influence of progestogen-estrogen preparations.

Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.

In breakthrough bleeding, and all irregular vaginal bleeding, consider nonfunctional causes. Adequate diagnostic measures are indicated in undiagnosed vaginal bleeding.

Carefully observe patients with a history of psychic depression and discontinue the drug if severe depression recurs.

Any possible influence of prolonged Ovulen therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study.

A decrease in glucose tolerance has occurred in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be observed carefully while receiving Ovulen.

Because of the effects of estrogens on epiphyseal closure Ovulen should be used judiciously in young patients in whom bone growth is not complete.

The age of the patient constitutes no absolute limiting factor, although Ovulen therapy may mask the onset of the climacteric.

The pathologist should be informed of Ovulen therapy when relevant specimens are submitted.

Adverse Reactions—A statistically significant association has been shown between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: cerebrovascular accidents, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, breast changes (tenderness, enlargement, secretion), change in weight, changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post partum, cholestatic jaundice, migraine, allergic rash, rise in blood pressure in susceptible individuals, mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme and nodosum, hemorrhagic eruption, itching. The following laboratory results may be altered by oral contraceptives: hepatic function: increased sulfobromophthalein and other tests; coagulation tests: increase in prothrombin, Factors VII, VIII, IX and X; thyroid function: increase in PBI and butanol extractable protein bound iodine, and decrease in T^3 uptake values; metyrapone test; pregnanediol determination.

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References: 1. Inman, W. H. W., and Vessey, M. P.: Brit. Med. J. 2:193-199 (April 27) 1968. 2. Vessey, M. P., and Doll, R.: Brit. Med. J. 2:199-205 (April 27) 1968.

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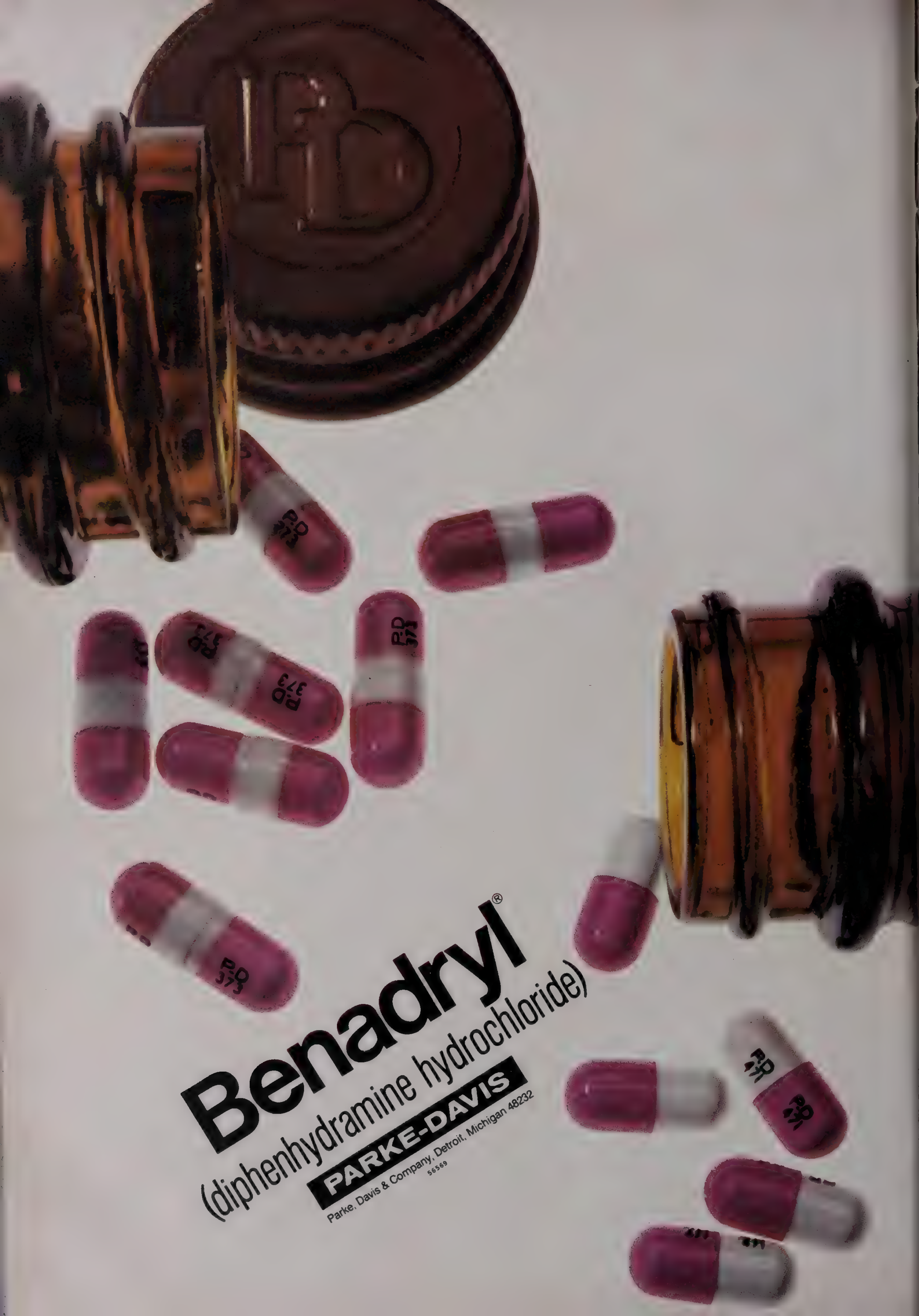
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Editorials

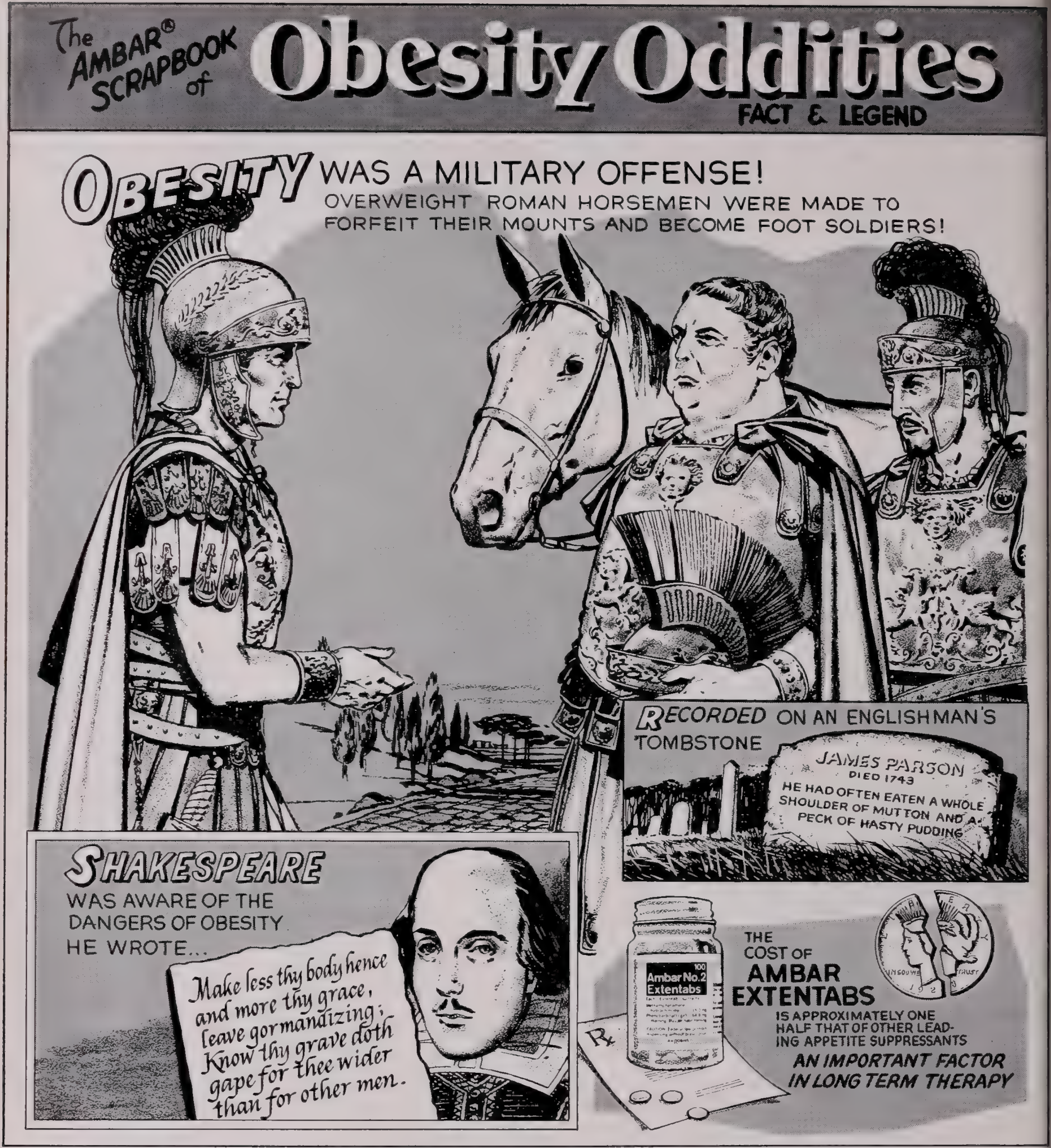
Fifty Years Ago

FIFTY YEARS AGO Dean Lyon could deal with his responsibilities in the Medical School and still have time to relate closely with the faculty and students. I remember him as a warm, genial man, easy to talk to. Not until several years later did Dr. Richard Scammon become involved in the affairs of the medical students and administration. Dr. Scammon supervised my graduate thesis, which involved statistical theory, foreign to me, which he tried (in vain) to clarify. He was an excellent teacher, a liberal thinker and philosopher, well liked by our class. Dr. Jackson was Head of the Department of Anatomy. He was a reserved person with a deep concern about students, which I recognized when I later taught under him in histology and neurology.

It is my duty and privilege this year to write the annual MINNESOTA MEDICINE editorial in honor of the newly elected members of the *Fifty Year Club* whose biographies and photographs appear elsewhere in this issue. [All the physicians—indeed all the citizens of the State of Minnesota—join the editors in honoring this distinguished group of physicians who have contributed so much to the welfare of the people of Minnesota. Ed.]

Names very familiar to me are: Dr. Scott in Physiology, Dr. Herschfelder in Pharmacology, Dr. Downey in Hematology, Dr. Bell in Pathology, Dr. Rowntree in Medicine, Dr. Moore in Surgery, Dr. Sweitzer in Dermatology, and Drs. Hamilton and McKinley in Neurology and Psychiatry. I recall the many legislative sessions Dr. Hamilton had to attend before he succeeded in adding an in-patient service in psychiatry, and it was not until many years later that the in-patient service in child psychiatry was added. The names of Doctors Rodda, Schultz and Sedgwick are fondly remembered, as I became a graduate student in pediatrics.

During our senior year in medicine many in our class served as junior interns in hospitals, depleted of regular interns because of the First World War. We were all in our senior year in the Student Army Training Corps. Those who were junior interns did not have to live in a special building near the campus reserved for this training. Those who served as interns attended lecture classes one or two days a week. We had not been assigned soldier's uniforms; so when we learned one day that we had to wear uniforms in order to be discharged from military service at the close of the War, we were hurriedly outfitted. There was little concern about hat size or sleeve length or trouser size, with the result that when we lined up for inspection, our classmates, the real soldiers, let us know in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no uncertain terms what an impression we made.

My senior internship was in internal medicine at the University Hospital, where I worked with Doctors Rowntree, Rizer and Hamilton. This provided an excellent opportunity because of small case loads from which to learn the fundamentals of medicine.

Graduate work in pediatrics brought us close to Doctors Seham, Anderson and Taylor. The outpatient department was in Millard Hall where I initially became acquainted with the role of social case workers. For the first time I learned that a group of professional workers involved themselves deeply with the emotional problems of children and families, and I was profoundly impressed. There was one social worker for the outpatient department in pediatrics, and she was very happy when I expressed a real interest in the behavioral aspects of the child and the family. Part of my fellowship was at the Mayo Clinic where, the year before, Doctors Helmholtz and Amberg headed this new service in pediatrics. The Mayo Clinic, incidentally, had become a part of our graduate school in medicine during our enrollment in the medical school.

The last year of my fellowship was at the Minneapolis General Hospital where Dr. Huenekins was Chief of Staff of Pediatrics. I had admired him as a teacher and looked forward to working with him. It was through his influence that my work in child psychiatry received its main thrust. In his capacity as Director of the Infant Welfare Clinics in Minneapolis, he introduced behavior clinics for the pre-school child and should be identified as one of the pioneers in the study of emotional problems of children in America. He later turned over this work to me and moved into other fields of research that interested him. Much of his career was devoted to introducing pilot studies involving the relationship between physical illness and psychosocial problems.

In the early 1920s, Dr. John Anderson came to the University as Director of the Department of Child Welfare under a Rockefeller Grant. Dr. Florence Goodenough was also a member of the staff and did much of her original research there. During this time Dr. E. K. Lashley was doing a great deal of his research work on the brain, particularly with reference to cerebral localization centers.

In 1923 Dr. Lawson Lowrey brought the Demonstration Child Guidance Clinic to the University for one year. This was under a grant from the Commonwealth Fund and provided us with the knowledge needed to set up the Amherst Wilder Child Guidance Clinic in St. Paul and the Child Study Clinic under the Department of Education in Minneapolis.

In those days interns received no salaries; fellowship stipends in child psychiatry began at $600 a year and went up to $900 in the third year. Two days' hospitalization with the flu in 1924 set me back a total of $18.00. A well built attractive house could be constructed at that time for $9,000. The street-car fare to the University was a nickel, and one could sit in the Minneapolis Orpheum Gallery on 7th Street for 15 cents. To the credit of Spearmint Chewing Gum, even in those days a package of gum cost only 5 cents, as it still does today.

Hyman S. Lippman, M.D.
St. Paul, Minnesota

Not Overpopulated

In the light of vitamin-conscious today, we wonder how mankind actually kept going before we moderns happened along. Consider that orange juice was once used in the West Indies to polish floors; pineapples first sold in London for twenty dollars apiece; in the days of Henry VIII, vegetables were considered unfit for humans and were fed to pigs; lemons were used by the ancient Romans to keep away moths.

Ladies Home Journal

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Advances in the Management of Hodgkin's Disease*

In recent years the long-held assumptions that Hodgkin's disease is usually of multicentric origin and that patients with this malady are rarely cured have been challenged. Newer approaches to its pathologic classification help the clinician determine which patients with Hodgkin's disease have the best prognosis. Those without systemic symptoms or whose lymph node biopsies show lymphocyte predominance or nodular sclerosis frequently have disease of limited extent. Adequate radiotherapy shows promise of curing a high percentage of such patients. Retrospective studies appear to indicate that a tumor dose of 3,500 to 4,000 rads is necessary to permanently eradicate Hodgkin's disease from any given site, but it is possible that patients with these two more benign forms of the disorder may be cured with a smaller dose of radiation.

Adequate clinical staging of the extent of involvement is essential to rational planning of therapy. Lymphangiography is of great help in detecting occult involvement of the para-aortic and iliac lymph node chains and is now routinely performed in many centers as part of the initial assessment of patients with apparently localized disease, prior to starting treatment.

Patients with more advanced stages have traditionally been treated with single oncolytic† agents. Although worthwhile palliation is often achieved, the remissions are often of short duration. Cooperative therapeutic trials are now in progress, comparing this standard drug treatment with a regimen employing multiple chemotherapeutic agents used in combination or sequence. Preliminary reports indicate a greater rate of prolonged remissions, without a prohibitive increase in morbidity due to drug toxicity, using the multiple-drug technique. Other clinical trials are exploring the usefulness of systemic chemotherapy, followed by focal radiotherapy to areas of residual disease, as initial treatment for patients with disseminated disease.

The physician caring for a patient with Hodgkin's disease can now expect from the pathologist more useful information to aid prognosis. Careful clinical assessment, aided by lymphangiography, will stage the extent of disease as a prelude to treatment planning. Wide-field, high-dose radiotherapy will permanently arrest the disorder in a high percentage of patients with localized disease. Newer concepts of chemotherapy may offer more prolonged remissions for those with disseminated disease. Never has the outlook for many patients with Hodgkin's disease been brighter!

Joseph M. Kiely, M.D.
Rochester, Minnesota

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*Maruyama, Y.: Hodgkin's Disease: Current Views on Management. Minnesota Med. 52:575, 1969.

†See Test Your Word Score Page 1087.

Vascular Compression of the Distal Duodenum*

Compression of the third portion of the duodenum by the superior mesenteric vessels is a well-known clinical entity that is practically never seen by clinicians. In one series of x-ray examinations of the upper gastrointestinal tract one film in 164 revealed such vascular compression. Either this incidence is inordinately high; or the examiners were inordinately astute. Perhaps if the x-ray signs were more diligently searched for in appropriate pictures, more cases would be discovered. Since medical treatment will produce relief in almost all patients, it is important that the condition be discovered when it is present. In the rare case in which surgical treatment becomes necessary, duodenojejunostomy would seem to be a more logical procedure than gastroenterotomy.

Farrell S. Stiegler, M.D.
Minneapolis, Minnesota

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*See page 1055.

Photo professionally posed.

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Warnings: Acute anaphylaxis (may prove fatal unless promptly controlled) is rare but more frequent in patients with previous penicillin sensitivity, bronchial asthma or other allergies. Resuscitative (epinephrine, aminophylline, pressor amines) and supportive (antihistamines, methylprednisolone sodium succinate) drugs should be readily available. Other rare hypersensitivity reactions include nephropathy, hemolytic anemia, leucopenia and thrombocytopenia. In suspected hypersensitivity, evaluation of renal and hematopoietic systems is recommended.
Precautions: In suspected staphylococcal infections, perform proper laboratory studies including sensitivity tests. If overgrowth of nonsusceptible organisms occurs (constant observation is essential), discontinue penicillin and take appropriate measures. Whenever allergic reactions occur, withdraw penicillin unless condition being treated is considered life threatening and amenable only to penicillin. Penicillin may delay or prevent appearance of primary syphilitic lesions. Gonorrhea patients suspected of concurrent syphilis should be tested serologically for at least 3 months. When lesions of primary syphilis are suspected, dark-field examination should precede use of penicillin. Treat beta-hemolytic streptococcal infections with full therapeutic dosage for at least 10 days to prevent rheumatic fever or glomerulonephritis. In staphylococcal infections, perform surgery as indicated.
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Hospital-Acquired Infections*

THE AVAILABILITY of potent antimicrobial agents has resulted in dramatic improvement in the results of treatment of infections which, in the pre-antibiotic era, were associated with high mortality. Lobar pneumonia, erysipelas, streptococcal bacteremia, and bacterial meningitis are often curable infections if properly treated. It has become evident, however, that progress in the treatment of various malignant diseases has resulted in the survival of patients with severe impairment of host defense mechanisms against infections by organisms of the Enterobacteriaceae family. Leukemic patients are especially susceptible to such infections. The danger of a hospital-acquired infection is further enhanced in gravely ill patients by a number of medical technical devices which now have become well-established tools in the diagnosis and treatment of such patients. The indwelling urinary catheter is well appreciated as a potentially dangerous factor in the causation of cystitis, acute pyelonephritis, and bacteremia.

A number of modern devices now commonly used must be looked on as vehicles for the invasion of microorganisms. To name only a few, there are the intravenous plastic needle which often is left in place for too long a time, the intravenous catheter for monitoring of the central venous pressure, and the intravenous wires of the extracorporeal pacemaker. Life-threatening bacteremic episodes may be the result of these otherwise beneficial modern devices. A major problem, potential pulmonary infection, is caused by the use of mechanical respirators. Fatal cavitating pneumonias have resulted from the use of such instruments when contaminated with *Pseudomonas* which easily grows in the nebulizer compartment. The presence of foreign bodies, such as an artificial heart valve, a pacemaker, or a ventriculoatrial shunt catheter, makes it next to impossible to eradicate an infection which has settled in an area immediately adjacent to such a device.

Besides microorganisms belonging to the Enterobacteriaceae, *Staphylococcus aureus* is the main bacterial invader under the circumstances of iatrogenic manipulation. The article by Myung-Hi Kim Ho and associates emphasizes the importance of infections in surgical patients. It is clear that the prophylactic use of antimicrobial agents is a poor substitute for strict aseptic techniques and the careful, regular inspection and monitoring of intravenous sites and of the many types of apparatus which are connected to the acutely and chronically ill patient.

Paul E. Hermans, M.D.
Rochester, Minnesota

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* See page 1067.

Epilepsia Cursiva Syndrome

Episodic alteration of consciousness associated with running characterizes this syndrome. Sisler and his associates described the condition in nine patients who had either grand mal or psychomotor epilepsy. The running may be coordinated, but it is inappropriate to the reality of the situation. Consciousness may be clouded to a variable degree. Electroencephalograms showed a typical epileptic pattern of disordered rhythm with temporal spikes. Personality types varied, and many of the patients had conflicts in relation to members of their family. Sisler and his associates suggested that these conflicts acted as precipitating factors in the conditions and that the running was an expression of the conflict. Anticonvulsant medication combined with superficial psychotherapy of a reassuring and explanatory type resulted in seizure control and decrease in behavior problems.

Durham, Robert H.—Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York

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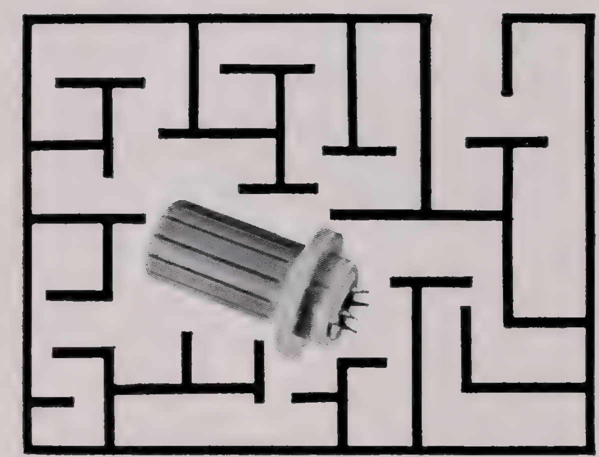

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Early Recognition of Acute Suppurative Arthritis

EARLY RECOGNITION remains the most important factor in the successful treatment of acute suppurative arthritis. In the small infant this may indeed be difficult. However, early diagnosis and institution of proper antibiotic therapy can be made only if joint aspiration is carried out as soon as septic arthritis is suspected. This should be considered an emergency procedure, just as we consider lumbar puncture for the establishment of a diagnosis and proper therapy of meningitis. However, the procedure should be carried out by persons properly trained in joint aspirations and, therefore, is primarily done by orthopedists.

The duration of antibiotic therapy after the diagnosis of bacterial arthritis has been made remains open to speculation. Gustilo and Amren,* in their article on acute suppurative arthritis in this issue, mention that the oral administration of antibiotics may need to be continued up to 12 months. This may seem excessive, and one wonders whether a diagnostic joint aspiration to determine sterility of the synovial fluid might not be considered to provide a basis for the decision to discontinue antibiotic therapy.

Gunnar B. Stickler, M.D.
Rochester, Minnesota

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*Gustilo, R. B., and Amren, D. P.: Acute Suppurative Arthritis in Children. Minnesota Med 52:219, 1969.

First Steps in the Development of a Computer-Based Laboratory Information System*

IN RECENT YEARS significant strides have been made in the performance of certain diagnostic procedures. The speed and accuracy of many laboratory tests have been increased by the introduction of automated techniques; however, techniques for processing laboratory data and transmitting them to the medical record remain largely unchanged and are becoming important limiting factors in the continued growth of laboratory technology. As the practice of medicine increases in complexity, the potential usefulness of computers becomes more and more evident, and one of the most promising medical computer applications is in the handling of clinical laboratory data. The more cogent reasons to undertake the development of automated laboratory information systems include: (1) increasing number of laboratory tests per patient work-up, (2) increasing cost and scarcity of medical technicians, (3) increasing role of computers in the performance of laboratory tests, (4) decreasing cost of test performance versus a stable or increasing cost of handling data, (5) centralization of medical services and the growth of regional medical concepts, and (6) increasing demand for medical services consequent to rapidly increasing populations and the extension of health care to larger numbers of people.

Many benefits should accrue from a computer-based laboratory information system; a few are self-evident, but documentation of most must await first-hand experience with functional systems. Monetary benefits in the form of personnel savings have been emphasized and should be realized; however, preliminary analyses indicate that such financial gains will be eroded significantly by the developmental and operational costs of an automated data-handling system. Although the nonpecuniary perquisites are more difficult to quantify than projected financial savings, they promise to exert a more dramatic impact; and they should greatly exceed the expected improvement in transporting a test result. Such

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*Fallat, R., and Strom, R. L.: Basic Concepts in Computer Science for Laboratory Physicians, and Fishman, N., and Strom, R. L.: On-Line Clinical Laboratory System. Minnesota Med 52:847, 1969.

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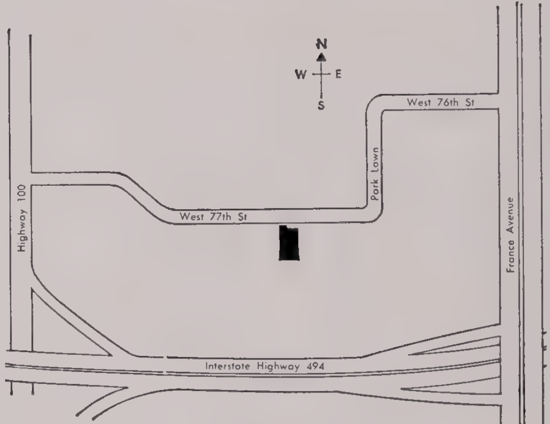
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benefits include: (1) elimination of the need to file, store, and retrieve paper reports; (2) reduction of errors by decreasing manual transcriptions and replacing handwritten, often illegible reports by computer-printed information; (3) making laboratory results immediately available to all potential users; (4) facilitation of quality control by means of computer monitoring; (5) increased sophistication of laboratory test-report formats for clinical, investigative, and educational purposes; and (6) stimulation of technologic growth in the form of increased automation of test procedures.

Scattered attempts are being made to computerize the processing of medical information generated in laboratories; but most operational or developing systems deal with a limited number of tests in one or more laboratories (for example, hematology, biochemistry, or surgical pathology), and few have been designed as components of a complete medical information system. In general, only simple numeric information has been considered, solutions have usually been sought from existing hardware, and the need to handle and maintain some paper records persists. Although studies to date have emphasized the potential advantages inherent in an automated laboratory information system, many important questions remain unanswered, and the first steps in this direction should be cautious ones. The excitement and glamour surrounding a computer-based operation are not adequate justification for its existence. In fact, such a laboratory information system could actually constitute a step backward if it increased the likelihood of error consequent to an additional human transcription or if the test-report format was no longer acceptable to the user. Although the mere presence of a computer in a laboratory can create an aura of accuracy and efficiency, it does not automatically assure fewer errors or increased productivity. If a computer is incorrectly programmed, it will provide incorrect information. Because of the many, varied, and complex laboratory information-handling problems, ready-made information systems are apt to fit poorly and some hand-tailoring is needed.

There is compelling support for the contention that the full benefits of a computerized laboratory information system will be achieved only when it functions on-line as an integral part of a complete medical information system. However, the inchoate state of automated medical information systems demands solutions to many general problems before an integrated holistic* approach becomes practical. In addition to the transport of a report from its place of origin to a file or a user, other problems that must be solved include identification of the test, patient, and specimen; generation of forms; report format development; message verification; computer reliability and backup; quality control of machines and operators; data storage and retrieval for clinical and research purposes; and automatic generation of special reports. It is noteworthy that many of these information-handling problems have complex interfaces with others now facing the medical profession—for example, registration, scheduling, and billing.

There is no longer doubt that computerized laboratory information systems are feasible and desirable. However, the developmental road is rocky and characterized by pitfalls and dead-end pathways; it is already strewn with evidence that some have failed to plan their journey well. The first steps should be taken only after the route has been judiciously chosen; individual requirements and problems must be recognized and carefully defined. It is essential that physicians participate actively in these initial decisions as well as in all phases of the development of computer-based medical information systems, for they alone can delineate the medical problem and determine if a particular solution is medically acceptable. Such participation does not require that the physician possess expertise in electronics or engineering. Lastly, it should be kept in mind that the ultimate goal is a computerized laboratory information system which functions as an integral component of a complete medical information system. One can only speculate as to when this goal will be achieved, but it can be predicted with reasonable certainty that it will be reached; medicine will then realize the full potential usefulness of computers. We must begin now in order to meet successfully the challenges of the future.

James W. Linman, M.D.†
Rochester, Minnesota

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*See Test Your Word Score Page 1087.

†Consultant, Sections of Clinical Pathology and Medicine, Mayo Clinic; Professor of Medicine and Clinical Pathology, Mayo Graduate School of Medicine (University of Minnesota).

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Letter to the Editor

In his editorial regarding Dr. Lenggenhagers' paper in the January 1969* issue, Dr. Ronald L. Linscheid wisely suggested the possibility of using a conservative alternate program for treatment.

A modification of this injection technique combining hydrocortisone and Xylocaine can sometimes be more effective than the perfusion of the involved area.

By carefully introducing a 22 needle at the distal palmar crease, the involved tendon can be identified. The tip of the needle is withdrawn a few millimeters and 2 to 3 cc. of the combined solution introduced. Frequently with this technique a palpable and audible "click" can be elicited and the tendon sheath mechanically lysed from the tendon.

By using this hydrostatic technique, a satisfactory lysis may be obtained to afford permanent relief and preclude surgical decompression.

Walter Indeck, M.D.
Minneapolis, Minnesota

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*See page 81.

Test Your Word Score

Ethanol—*ethyl alcohol* (page 1051).

Birefringent—*doubly refractive* (page 1052).

Pincers—*a grasping organ or pair of organs* (page 1055).

Patulous—*open, distended* (page 1056).

Café-au-lait—*light brown color* (page 1061).

Enteric—*relating to the intestine* (page 1070).

Oncolytic—*destroying tumor cells* (page 1079).

Holistic—*referring to man as a total entity, a functioning whole* (page 1085).

Stellectomy—*division of the cervical sympathetic cord above the stellate ganglion* (page 1121).

Hygroma—*a sac, cyst, or bursa distended with fluid* (page 1127).

Derivatively Speaking

Anthrax—from Greek *anthrax* (coal)

The Editor's Soliloquy

Social Dereliction

We wonder whether some of the social programs of the Federal Government are not inadvertently raising a breed of parasites. In Kentucky, Medicare and Medicaid make government-financed medicine available to the majority of the populace. Ten physicians last year collected more than $50,000 each from that state for Medicaid service, and the total Medicaid budget for Kentucky for the year was a staggering $48,000,000.

In a village of 800 in Letcher County near the Virginia border a pharmacy was reimbursed $328,290 from the State for filling Medicaid prescriptions, and another pharmacy owned by the same man collected an additional $125,950.

To be sure, patients, not doctors, were determining the frequency of office visits and, though patients do not usually consult a doctor for the common cold, in Kentucky many Medicaid patients did just that at an average cost to the State of about $11.50 per visit.

Some individuals consulted a physician as often as thirty times in two months. The approved government practice is a charge of $10 for the first visit and $5 for each subsequent visit for any one complaint.* And believe it or not, some patients are so extraordinarily versatile as to present a different ailment on each appearance in the doctor's office.

What a fertile field for exploitation: the patient's versatility, the druggist's passivity and the venality of the unscrupulous doctor correlating and operating reciprocally to the benefit of all. Fortunately these isolated instances do not represent the practice of most physicians.

It would be amusing, were the implications not so pernicious, to scan the records of some of the inveterates to see what maladies they reported themselves to be suffering from and what treatments or medication they received. We wonder: did any of them perchance run out of ailments? And if so, did they then run the gamut all over again?

The State of New Mexico has found it necessary to suspend Medicaid because it has run out of money. Two dentists made more than $90,000 each in 1968 for treating welfare patients. One osteopath billed Medicaid for seeing a patient 100 successive days with the charges varying from $6.18 to $81.37 for each visit. Twelve thousand dollars was expended to pay taxi fare for the patients to and from physicians' and dentists' offices.

In Florida a general practitioner was paid $191,000 for Medicare treatments in a single year. A Georgia surgeon collected $131,000. Beginning in June the names and addresses of doctors who made more than $25,000 will be on file in the Senate. Eleven states have so far chosen to stay out of the costly program which is draining state funds at unanticipated rates.†

Of the nineteen million who are on the voluntary Medicare doctor program, which provides a revenue to the Federal government of $1,824,000,000 to pay for doctors' fees, it would be interesting to know what portion of this revenue has been spent for administration of the program.

In the State of Minnesota the Northlands Regional Medical Program, Inc., a federally sponsored organization, was allotted $1,209,910 for the purpose of making surveys into the far corners of the state. They have a full time staff of six coordinating experts, a suite of offices and a board of medical men who receive a small honorarium for each board meeting. As far as anyone can determine over the three-year period of their existence, not one penny has been spent for medical or surgical care of a patient. Contrary to the impression that one gains from reading their bulletins, surely an infinitesimally small number of practicing physicians are of the opinion that we are living in a medically backward state or that even the most remote and inaccessible corners of the state are in dire need of "the latest medical knowledge from research centers" in order that it can be brought to "the patient's bedside."

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*National Observer, April 28, 1969.

†Science News, 95:497, May 24, 1969.

Such inordinate demand for medical aid is not a demonstration of the need for it but rather an illustration of the abuse to which an intended social benevolence can be put.

The honorable physician and pharmacist know better than to say cynically: If we don't provide the service, someone else will; but such may be the dilemma in which we may eventually find ourselves and from which we may discover it is too late to extricate ourselves. Complacency and apathy are insidious factors that can slowly and silently corrupt the strongest of institutions.

Patients who are demanding and doctors who are prescribing tranquilizers, sedatives, pain-killers, dependency-producing drugs, or even just placebos may be inadvertently propagating a nation of derelicts, like the feudal lords of China who, centuries ago, addicted a nation and literally destroyed it.

Carl O. Rice, M.D.

You May Be Right

IN HIS CURRENT soliloquy the editor has seen fit to cover a wide spectrum of social dereliction with the implication that physicians and patients alike are prone to take advantage of government programs even to the extent of outright cheating. Appropriately, he recognizes that gross abuses under Medicare and Medicaid are restricted to a small minority of physicians.

One may question whether overcharging and unnecessary and excessive service, exposed by government auditing, are confined to government-sponsored plans. To the unbiased observer, the conclusion that this revelation constitutes a grave challenge to the medical profession to police its own house may seem as justified as a condemnation of programs which open up the public till. This conclusion is valid whether the observer believes the basic philosophy of "social insurance" is desirable in whole or in part. Most responsible physicians will probably support legislation which will allow the government to prosecute those vendors of health care who are guilty of fraud in Medicare and Medicaid. Peer review of practices and charges which are questioned by third party carriers is a policy in many medical societies which seems to be working satisfactorily; and utilization review mechanisms, approved now for several years by the American Medical Association, are functioning smoothly in many hospitals.

For those who may be interested, HEW reports that for the fiscal year ending June 30, 1968, administrative costs for Medicare hospital insurance were 2.1% of benefits and for Part B, 10.3%. These figures are comparable to those reported by privately operated hospital and medical insurance programs.

Northlands Regional Medical Program has developed an organization which some may consider a bureaucracy, but at this time most of those who have knowledge of the program see the potential for many desirable accomplishments. All segments of the health care delivery system are in better communication than ever before. In Minnesota the State Medical Association has been represented in every stage of development of the regional medical program, and the voluntary health associations, particularly the Minnesota Heart Association, have led the way in the development of projects which have been well received by practicing physicians. If Minnesota's regional medical program fulfills its obligation, the best available knowledge will emanate from many centers in Minnesota, not just from the "research centers." Those of us who practice medicine in this State have every right to feel that our services are among the very best; but, at the same time, not one of us should be willing to admit that there is no room for improvement or that we cannot learn something of practical importance from the resources available within our State.

The editor laments the fact that no moneys of the regional medical program have been spent on medical or surgical care for patients. Perhaps he should be reminded that the law prohibits such use of funds, a provision for which organized medicine fought.

J. M. Stickney, M.D.
Rochester, Minnesota

Old Doc Hess says: Most evils need no reviewing by a committee, they need only to be quit.

The Heart Besieged

Surgeon Yushkova handled an absolutely astounding case. She performed an operation that has few to equal it in the history of cardiorrhaphy.

While examining a revolver a nineteen-year-old girl inadvertently pressed the trigger. The bullet passed through her heart. Certain symptoms helped to determine that it penetrated the abdominal cavity. Two hours later the girl was put on the operating table.

Yushkova made her first incision. She found the left ventricle pierced, and sutured it. But a gurgling sound in the thorax every time the patient inhaled showed that the pleura was also perforated, and Yushkova sutured it too. The abdominal cavity was opened up next, to extract the bullet. The surgeon found a hole in the diaphragm, and sutured it as well. Then she discovered that the liver was damaged, and sewed it up, and also sewed up the large intestine below the liver, which was also punctured. Finally, Yushkova located and extracted the bullet.

Although the patient's condition had appeared hopeless from the first, Yushkova stubbornly repaired damage after damage. She did not give death the benefit of even the slightest chance.

A month after the operation the young woman was discharged from the hospital.

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*L. F. Friedland, M.D.: The Achievement of Soviet Medicine, edited by W. Horsley Gantt, M.D., 1961.

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References: 1. Gardner, H. L.: J. Miss. M.A. 8:529, 1967. 2. Porter, P. S., and Lyle, J. S.: Arch. Dermat. 93:402, 1966. 3. Walsh, H.; Hildebrandt, R. J., and Prystowsky, H.: Am. J. Obst. & Gynec. 93:904, 1965. 4. Vaginitis and the Pill: J.A.M.A. 196:731, 1966. 5. Guerriero, W. F.: South. M.J. 56:390, 1963. 6. Seelig, M. S.: Am. J. Med. 40:887, 1966. 7. To-day's Drugs, New York, Grune & Stratton, Inc., 1965, p. 316. 8. Gray, L. A., and Barnes, M. L.: Am. J. Obst. & Gynec. 92:125, 1965. 9. Salerno, L. J.; Ortiz, G., and Turkel, V.: Vaginitis: A Diagnostic and Therapeutic Approach, Scientific Exhibit, presented at the 115th Annual A.M.A. Convention, Chicago, Illinois, June 1966. 10. Walsh, J. C.; Sheffery, J. B., and Wilson, T. A.: Med. Ann. D.C. 37:358, 1968. 11. Nugent, F. B., and Myers, J. E.: Pennsylvania Med. 69:44, 1966.

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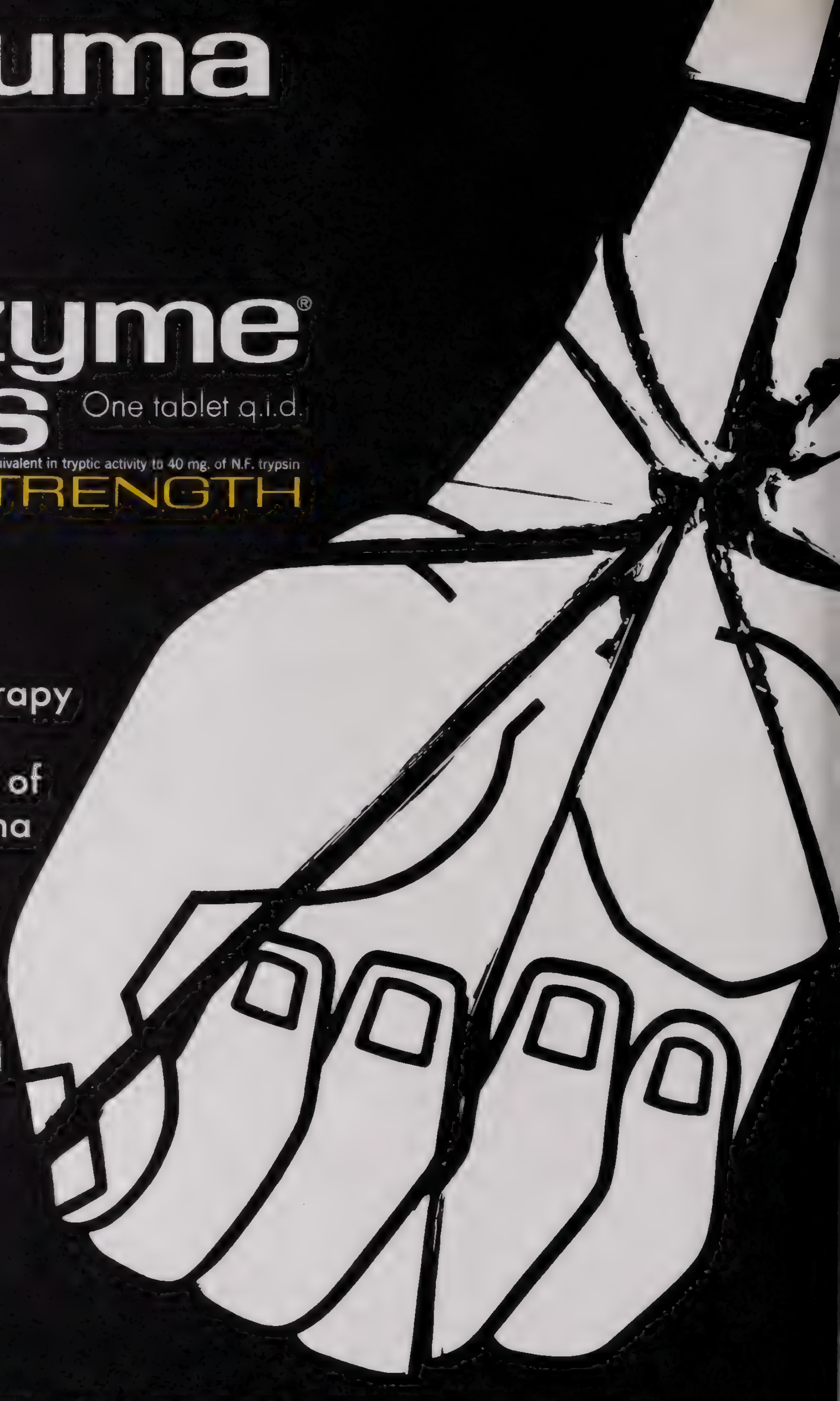

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The presentation of certificates and pins to Minnesota physicians who have engaged in the practice of medicine for 50 years has become an impressive highlight of each Annual Meeting. According to custom the presentations are made during the course of the Annual Banquet. Few who have witnessed these ceremonies soon forget the setting of such an occasion at which these colleagues with a half century of medical practice to their credit so alertly respond to the roll call.

The custom of honoring Minnesota physicians who have served their patients and communities for a half century was established in 1942. Forty-one physicians were honored at the first ceremony. This group also included those who had passed the 50-year mark prior to 1942.

To be eligible for this award a doctor must have spent the majority of his 50 years practicing medicine in Minnesota.

In 1969 eighteen doctors were added to the membership in this distinguished club.

If I were asked what event in my life had the greatest influence on my medical career I think it would be the receipt of the notification that I had been appointed a Fellow in Medicine by the Mayo Foundation.

The opportunity to take histories of, and do physical examinations on large numbers of patients is an unparalleled one. Especially so when one's tentative conclusions were promptly checked by the results of the laboratory tests, and the opinions and findings of consultants, surgeons and pathologists.

Arlie R. Barnes, M.D.

There were many amusing incidents along the way. In due time I became a member of the graduate committee of the Mayo Foundation. A part of our duties in conjunction with representatives of the Graduate School of the Medical School was to examine candidates for advanced degrees upon the completion of their thesis. A young doctor of Irish descent was being examined as a candidate for the M.S. degree. His minor was pathology. His examiner from the campus of Minnesota was reputed to be a "tough" examiner. His opening question was, "If I gave you a bushel basket full of spleens obtained at necropsy, describe the pathological conditions you might encounter." The candidate, obviously and justifiably nonplused, did not answer for about 15 seconds and then asked, "Doctor, may I be permitted to section those spleens?" When the answer was "Yes," there was a longer and more embarrassing pause and the candidate remarked, "I can't see that it helped me much." After the laughter subsided a less comprehensive question was substituted and the examination went on to a totally satisfactory conclusion.

My contacts with physicians in Minnesota, in societies, at the University or in consultations have been gratifying ones. As I look back over my experience at the Mayo Clinic I can think of no pleasanter environment in which to spend my years as a student and as a practitioner of medicine.

Donald H. Daniel, M.D.

Until his retirement in 1952, Dr. Donald H. Daniel, Minneapolis, was a general practitioner in Minneapolis. He was born in 1892 and graduated from the University of Minnesota in 1920 with an M.D. degree. He interned at Louisville General Hospital in Louisville, Kentucky, from 1919 to 1920. Upon moving to Minneapolis he became a member of the Northwestern Hospital staff.

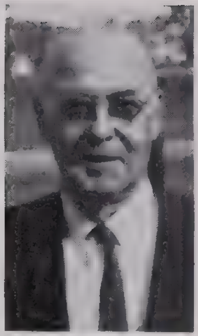
It was in 1908 that a bright-eyed and bushy-haired boy entered North High School in Minneapolis, with the anticipation of becoming a mechanical engineer. After graduating, more definitive anticipation of the engineering career developed upon entering the University, enhanced further by obtaining a job in the drafting room of a manufacturing company which specialized in building sawmill machinery.

Claude J. Ehrenberg, M.D.

For a few months all went well until spring weather provided its enchantment. The drafting room grew increasingly warmer; the endless drawings and blueprints grew increasingly boring. Engineering was fast losing its enchantment. Fortuitously the president of the company had occasion to visit the drafting room and if he was not exasperated upon his arrival, he apparently quickly became so by the pert and saucy responses he received to his inquiries. Shortly thereafter the chief draftsman called the young engineer aspirant to his table and informed the young man that his services were no longer required.

That fall I matriculated at the University of Minnesota undetermined as to any type of career. There I came under the influence of the inestimable and memorable Dr. Sigerfoos during a course in animal biology. From there it was but a short step into the study of medicine.

The founder of the Fairmont Community Hospital, Dr. Victor H. Gardner, Fairmont, was graduated from Leander Clark College, Iowa City, Iowa, in 1917. He received his M.D. degree from the University of Iowa Medical School, also in Iowa City, in 1919. After he interned in obstetrics and gynecology at the University of Iowa Hospital Dr. Gardner practiced in Estherville, Iowa. Before moving to Fairmont he practiced in Dunnell and Waseca.



Victor H. Gardner, M.D.

Retirement from active practice made it possible for me to spend more time with previously neglected hobbies, but it also allowed so much free time that new interests seemed necessary. The opportunity, during all but the winter months, of having almost daily walks with two naturalists and an historian provided an excellent solution to the last problem. A new interest in wild flowers—a field big enough for several life-times of work—pleasantly supplements old interests in bird-watching and trout-fishing, and all these activities supply material for water-color painting. I can't think of a happier way to retire.

Samuel F. Haines, M.D.

Dr. Philip L. Halenbeck, St. Cloud, initiator of the St. Cloud Medical Group, was born in Medicine Hat, Alberta, Canada, in 1891. Forty-one of his 50 years of practice have been spent in St. Cloud where he still practices today. He graduated from the University of Minnesota in 1915 and obtained his medical education at Rush Medical College, Chicago, Illinois. He interned at St. Luke's Hospital in Chicago in general practice, then came to Minnesota and practiced for seven years in Crosby before moving to St. Cloud.

Philip L. Halenbeck, M.D.

Harlow J. Hanson, M.D.

A farm two miles south of Hutchinson in McLeod county was my birthplace in 1892. After preliminary schooling I entered the University of Minnesota for a B.S. degree, then the University of Illinois medical school, and received my M.D. degree in January 1919.

I began my practice in New London. In winter the only means of travel was horses and sleigh. One particular incident which is of particular satisfaction was when a patient was brought to my office (1922) who had gotten his knee in a circular saw while cutting wood. The patella was completely gone; the articular surfaces were nice and smooth except for saw dust. After debridement the muscle and soft tissue were sutured and the knee immobilized. It was quite a satisfaction to meet him on the street afterwards and hear him say: "Doc that knee is just as good as the other one."

I moved to Minneapolis in 1925. Besides my practice I was health officer for the City of Bloomington for 34 years and was awarded a certificate of merit by the city.

I live on the bluff of the Minnesota river in Bloomington with trees and brush, and we have many different birds, pheasants, pileated woodpeckers and a coon who comes up for his favorite food.

Just a remark about the snowmobile craze. I made a snowmobile in 1922 while in my country practice. A Ford car narrowed to fit bob-sled tracks, runners in front and back, and drive shortened for traction. I traveled many miles on it and it did very well. It has all been very satisfactory.

Frank G. Hedenstrom, M.D.

After my licensure in 1919, making me a fledgling doctor, I interned at St. Paul City and County Hospital. I experienced the second wave of the influenza epidemic and the subsequent high incidence of encephalitis. Diphtheria and scarlet fever with their complications were rampant.

The next year I spent in private practice at Braham, Minnesota, with Dr. Charles Swenson, and thereafter returned to the University of Minnesota on a Pediatric Fellowship. Following graduate work in pediatrics, I opened an office in Saint Paul and became involved in the communicable disease section of Ancker Hospital. Here I saw the sharp decline and control of diphtheria, scarlet fever, hemophilus, meningitis, rheumatic fever, and poliomyelitis.

In 1931 we had 189 cases of poliomyelitis and during the peak epidemic of 1946 we had 251 cases of poliomyelitis at Ancker Hospital. I have been on the Pediatric Staff at Gillette State Hospital observing the decline and control of the complications of poliomyelitis, tuberculosis of the skeletal system, and pyogenic osteomyelitis. I was Pediatrician for the Children's Home Society and the Family Nursing Service. I am certified by the American Board of Pediatrics, a fellow of the American Academy of Pediatrics, president of the Northwestern Pediatric Society and president of the Ramsey County Medical Society.

My avocations have been duck-hunting, swimming, and trout-fishing, and I anticipate walking a few more trout streams.

Charles Hymes, M.D.

Dr. Charles Hymes, well-known to his classmates, colleagues and friends as "Charlie," has been in active practice for forty-nine years, first as a general practitioner, and subsequently as a specialist in ophthalmology and otolaryngology.

He married Viola Hoffman, a graduate of the University of Minnesota, in 1930. They have two sons and seven grandchildren. Son Alan is a cardiac and thoracic surgeon, and Richard is a contractor and real estate operator.

Dr. Hymes' thesis for his Master's Degree in Ophthalmology concerned itself with the development and growth of the normal eye. The scleral flap cataract operation and the grooved enucleation implant, as well as the treatment of acute sinusitis with antibiotic solutions by the means of self-induced intranasal negative pressure, are some of his innovations.

Dr. Hymes and his wife enjoy traveling and have been to Europe and Israel several times in the past few years. They have recently returned from a trip to South America with the Minnesota Medical Association.

Don't tell me I look like Truman.

For over thirty years my wife and I have spent July and August in the mountains of Wyoming Jackson Hole and at Woods Lake in Western Colorado at 9500 feet. No one except some of the old timers about Camp had any idea that I was an M.D. Each summer I served as a veterinarian: on a pack trip some fifty miles back in the Wilderness, I operated upon one of our big pack horses which developed a huge abscess on his withers. Vets later told me that fistula on the withers was brucellosis, but apparently my technique was good and no one picked up the infection. To continue the illusion as a veterinarian, I treated cinch and saddle sores and infected wire cuts, checked joints and hoofs in limping horses, removed stones and on one occasion a penetrating horse shoe nail.

I also de-quilled three dogs who were unlucky enough to catch a porcupine. The last was a big Boxer. I blocked his jaws open with a stick on which he chewed very vigorously at first but soon stopped and just held his mouth open while I removed over 75 quills from his tongue, gums, nose and face. After it was over he came over and licked my hands. That is gratitude for you.

Perhaps this is a suggestion for some other poor physician on vacation to help him dodge the tourists seeking free advice.

Thomas J. Kinsella, M.D.

After fifty years of medicine I suppose I should want to retire, but I don't. My work in Child Psychiatry has been so pleasant and gratifying that it is difficult to picture myself leaving the field especially at a time when there is so much to be done. Social workers, clinical psychologists, educators, and many others with a dedicated interest in the social and emotional welfare of children have for forty years been a part of my working family. After thirty-seven years at the Amherst H. Wilder Child Guidance Clinic I am now doing consultation work and teaching at St. Paul-Ramsey Hospital and Medical Center and at Hennepin County Child Welfare.

I have been on the Board of the Joint Commission for Mental Health of Children for the past three years. This has offered me the opportunity of bringing to a head all that I have learned about the emotional needs of children and families, sharing with a large number of colleagues our experiences as clinicians in child behavior. The recommendations we are making to Congress will go a long way towards meeting unmet needs in our society.

Hyman S. Lippman, M.D.

Dr. Peter Arnold Lommen was born in Vermillion, South Dakota, in 1893 and graduated from the University of South Dakota Medical School in 1914. He immediately began his professional education which he completed at Rush Medical College in 1919.

He came to Austin, Minnesota, in January 1920 and has since been active in his professional work and in community service.

He was married to Corena Henry in 1923 and to them were born five children, four sons and one daughter. Two of the sons, Dr. Peter Arnold Lommen Jr. and Dr. Morris Leslie Lommen have followed in their father's footsteps being doctors in the same Lommen Clinic in Austin.

Dr. Lommen's talents and his generosity of spirit are revealed in the following enumeration of activities:

Member and three times president of the Mower County Medical Association; member of the staff of St. Olaf Hospital since its organization and three times president; honored on numerous occasions for medical research studies contributed to professional meetings and periodicals; charter member of Kiwanis, president in 1946, District governor with a record of perfect attendance for 42 years; member and director of Civic Music Association since its organization; member and director of the Chamber of Commerce; member of the first Austin Male Chorus; member and participant in Austin Oratorio Society; received the distinguished service award of the Minnesota Education Association for his integrity and ability to think and act on the basis of facts; nominated to the Hall of Fame in July 1968.

Peter A. Lommen, M.D.

Dr. W. Ray Shannon, Faribault, was one of St. Paul's first pediatricians. Born in 1893 in Duluth, he was a University of Minnesota graduate. Before beginning his practice in pediatrics, he worked in pathology in Montana. His special interest has always been diseases of the newborn and he is best known for his research in cyanosis and tetany in youngsters. He was one of the first staff members of the Family Nursing Service in St. Paul. In 1921 he became an assistant instructor at the University of Minnesota, and upon retirement in 1960 he became an assistant clinical professor of pediatrics there.

Carnot H. Sherman, M.D.

Born in South Dakota and grew up on a farm near the small town of Mt. Vernon. Attended high school in that community and then matriculated at the University of South Dakota as a premedical student and received the B.A. degree. Then finished training at Northwestern Medical School at Chicago.

After internship, went to Arizona for a short while and in 1921 took up practice at Marine-on-St. Croix, Minnesota, which at that time was the tail end of the "horse and buggy" days of the practice of Medicine.

Two years later moved to Bayport, Minnesota. Both of these towns are located on the beautiful St. Croix River and are quite a change from the almost treeless plains of South Dakota.

Six years later took graduate work at the University of Pennsylvania Graduate-School. Then seven years in North Dakota during the "hard" years with dust storms, grasshoppers and drought.

Returned to Bayport to practice and have remained here ever since. Activity has been that of general practice and considerable industrial work with the Andersen Corporation who manufacture windows and with other industries in the town.

Also was Attending Surgeon at the Minnesota State Prison for a number of years and later Chief Resident Physician in addition to private practice.

Adam M. Smith, M.D.

Looking ahead in 1919 when I graduated, 50 years seemed eternity; now looking back, 1919 seems like yesterday. Upon graduation, after a year's internship at Minneapolis General Hospital, I bought a desk and opened an office as a general practitioner. After five years of practice, I was affluent enough to take a trip to Europe, which included three months' study in Vienna. I came home to continue general practice, married and fathered one son.

The trend toward specialization prompted me to go back to Vienna and train in Internal Medicine, after which I returned just in time to fall victim to the 1929-31 depression. As I was sinking for the third time, I acquired a half-time industrial position caring for the 1500 postal employees of the Minneapolis Post Office.

This industrial work, plus my private practice, kept me very busy until 1959 when I retired from the industrial work. Five more years of private practice and I had had it. Turned my office-patients and problems over to my office companion and left on a fast plane to the Orient. The last five years have been five years traveling—reading—working at hobbies.

I have had many experiences and have seen many tragedies. It was always my desire to be understanding in the care of those who were seriously ill.

On the Mesabi Iron Range, when I first came to Minnesota, I received a phone call from a patient who stated that she was very ill. I drove to her home much quicker than she had expected and saw her run from the garden patch into the house. After knocking on the door I heard her call for me to enter, where I found her fully clothed under the covers in her bedroom. When I asked her to explain this strange situation she merely stated that payroll deductions had been made by the mining company and she wanted to get her money's worth.

Cyril M. Smith, M.D.

Dr. Knute A. Sporre, Fergus Falls, came to America from Sweden in his early adolescence. He was graduated from the University of Iowa College of Medicine and has been licensed in both Iowa and Minnesota. A surgeon, Dr. Sporre served southwestern Minnesota and northwestern Iowa in his early practice. Since 1959 he has been on the staff of the Fergus Falls State Hospital and is now chief physician of medical and surgical service there.

Knute A. Sporre, M.D.

Dr. Willard D. White interned at Cook County Hospital after graduating from Rush Medical College in 1918. Upon leaving Cook County Hospital and Chicago, he came to Minneapolis, to be an assistant to Dr. Robert Emmet Farr, an enthusiastic pioneer in local anesthesia. Dr. White assisted him for one year and then became associated with another surgeon, Dr. Archa E. Wilcox, for three years. He was appointed to the surgical staff of the Minneapolis General Hospital (now the Hennepin County General Hospital) after taking a Civil Service Examination and remained on the staff for many years.

In 1924 he married Evangeline Skellet of Minneapolis. They are still happily married and have two sons and eight grandchildren. Dr. White retired at 69. Due to angina he was encouraged to avoid the severe cold and strong winds of Minnesota and has been spending the last several winters in Pompano Beach, Florida where he can enjoy his hobbies of photography, fishing, boating, spectator sports, and just being lazy and being outdoors. He no longer plays regular golf but does a great deal of putting with friends in a weekly tournament. When he returns to Minneapolis in April, or soon thereafter, the ice is out of the lakes, grass is beginning to get green, leaves and blossoms appear, boats are put in the water, the fishing season opens, and there are grandchildren to take fishing and to play with. Dr. and Mrs. White never fail to be thrilled with "the miracle that is spring."

Willard D. White, M.D.

In Appreciation

It is with a feeling of sincere gratitude that we wish to acknowledge the valuable contribution of our technical exhibitors to the success of the Minnesota State Medical Association's 116th Annual Meeting. The Minnesota tradition for outstanding scientific meetings was unquestionably enhanced by these fine exhibits. We frankly recognize that continued participation by our exhibitors in future meetings is essential if we are to maintain this proud tradition. The firms listed below, through their participation in our 1969 Annual Meeting, have demonstrated a meaningful interest in the Minnesota State Medical Association and our Annual Meetings. We sincerely urge that all of our members join with us in expressing our appreciation to these firms and their representatives.

Delmar R. Gillespie, M.D.
President

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Curbstone Consultation

Splenectomy for the Diagnosis of Splenomegaly

QUESTION: Is splenectomy ever justified for a patient with splenomegaly in whom a complete diagnostic workup fails to reveal a cause for the findings?

ANSWER: An excellent article bearing on this problem was recently published.* In this series splenectomy was resorted to when other diagnostic measures failed. Fifty-two patients were managed in this way and a diagnosis was established through splenectomy in a majority of them. About one third of the patients were found to have malignant lymphoma, 25% congestive splenomegaly, 34% inflammatory or infiltrative disease; and 6% were found to harbor splenic cysts. This high diagnostic yield rate would seem to recommend splenectomy for the cases about which inquiry is made, providing the patient does not have some associated condition precluding major surgery.

Harold D. Kletschka, M.D.
Montgomery, Alabama

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*Hermann, R. E., DeHaven, K. E., and Hawk, W. A.: Splenectomy for the Diagnosis of Splenomegaly. Ann Surg 168:896, 1968.

Security

When God made the oyster, He guaranteed him absolute economic and social security. He built the oyster a house, a shell, to protect him from his enemies. When hungry, the oyster simply opens his shell, and food rushes in for him.

But when God made the eagle, He said, "The blue sky is the limit. Go and build your own house," and the eagle built on the highest mountain crag, where storms threaten him every day. For food he flies through miles of rain and snow and wind.

The eagle, not the oyster, is the emblem of America.

G.E. News

Classified Advertisements

Classified advertising rates are twenty (20) cents a word; minimum monthly charge $5.00; key number, fifty (50) cents additional.

Replies to advertisements with key numbers should be mailed in care of Minnesota Medicine, 375 Jackson, St. Paul, Minn. 55101.

WANTED: Physician for opening in busy established GENERAL PRACTICE in pleasant out-state location. Salary of $35,000.00 1st year. Write Minnesota Medicine-438, 375 Jackson, St. Paul, Minn. 55101.

GENERAL PRACTITIONER wanted to join well established practitioner in city of 6,000 and serving a population area of 18-20,000. Approximately 70 miles west of Minneapolis-St. Paul. Well-kept clinic building two blocks from the hospital. Fully accredited 85 bed hospital with a Resident Pathologist, Radiological Service, LPN School, X-ray Technician School and complete Physiotherapy Department. Short-term association on salary basis or long-term association with eventual partnership; will accept, consider and appreciate either terms. Please send short resume of your education and previous experience. For further information about this opportunity write: MINNESOTA MEDICINE 431, 375 Jackson, St. Paul 55101.

WANTED: General practitioner to join two young general practitioners in well-established practice in suburban St. Paul. Excellent office space with lab, x-ray, and emergency room. Salary negotiable, with an association leading to early partnership opportunity. Write MINNESOTA MEDICINE 412, 375 Jackson St., St. Paul 55101.

INTERNIST AND GENERAL PRACTITIONER wanted to join a five-man clinic group in Minneapolis. Complete laboratory and X-ray with board roentgenologist. Excellent hospital staff associations. Salary arrangement to start with, early partnership. Write MINNESOTA MEDICINE—289; 375 Jackson, St. Paul, 55101.

CANOE TRIPS—Complete relaxation in the Quetico-Superior Wilderness. Cruise, fish and explore, or base camp on remote lakes. Paddle, motor or fly in. Bring your family—return home completely rested. Cost only $9.00 per diem, $7.00 under 12. Write: Bill Rom, Dept. MM, Canoe Country Outfitters, Ely, Minnesota.

WANTED: Young General Practitioner to join 5 man general practice group. Services of General Surgeon and Radiologist immediately available. College town serving population of 22,000, 30 miles from Twin Cities. Contact Roland M. Hammer, M.D., River Falls Medical Clinic, River Falls, Wisconsin. Phone 425-5322.

WANTED: General Practitioner for staff physician on General Medical Service. Regular hours. Generous fringe benefits, including outstanding retirement program. Nondiscrimination in employment. For further information contact Chief of Staff, Veterans Administration Hospital, Des Moines, Iowa 50309.

THREE PHYSICIANS WANTED: Emergency room at St. Paul, Minnesota, June 1, 1969. 450 beds, expansion 600 beds, 1970. Minimum guarantee $25,000 per year. Work week 28 hours. Contact Thomas W. Votel, M.D. 612-488-6777.

OPPORTUNITY FOR CAREER in occupational medicine with large corporation. Multiple locations. Salary plus fringes. Immediate openings in three locations. Give resume. Write: MINNESOTA MEDICINE—432, 375 Jackson, St. Paul 55101.

THREE MAN group in North West Wisconsin Resort, State Conservation and Retirement Area needs two more physicians adequately to serve their practice. Facilities offered are three-room physician suites, X-ray and lab under AMT technician, RN-only nursing personnel. New accredited thirty-two bed hospital and forty-six bed nursing home. Deer and duck hunting, fishing within five minutes of town. Internist most needed; generalists welcomed. Will meet any reasonable salary request. Partnership after one year. Write: MINNESOTA MEDICINE—365; 375 Jackson St., St. Paul 55101.

ASSOCIATE urgently needed in busy general practice. Excellent clinic and hospital facilities. Salary open. Partnership after 1 year. Klefstad Clinic, Greenbush, Minn. Call collect: Lloyd H. Klefstad, M.D., Tele. 218—782-5275 or 4725.

GENERALISTS AND PSYCHIATRISTS—In accredited progressive 2000 bed mental hospital with approved psychiatric residency training program. Ideal living in active resort community located in Michigan's serene, scenic water-wonderland. Salary $22,550-$30,464 depending on qualifications. (Salary rates effective July 1, 1969.) Unparalleled retirement and fringe benefits. Contact M. Duane Sommerness, M.D., Superintendent, Traverse City State Hospital, Traverse City, Michigan 49684. An equal opportunity employer.

INTERNIST—Six physicians in corporate practice wish to increase service to area by adding general internist to its staff. Fringe benefits are available. Salary open. 150 bed open staff joint commission accredited hospital in community. Write: MINNESOTA MEDIINE—429, 375 Jackson St., St. Paul 55101.

MINNESOTA PROFESSIONAL CORPORATION with fringe benefits wishes to add a general practitioner. Full rights and privileges after one year. Joint commission accredited hospital, open staff. Write: MINNESOTA MEDICINE—430, 375 Jackson St., St. Paul 55101.

Continued to page 1148

The Viewing Box

Atelectasis of Lung following Automobile Accident

THIS 16-YEAR-OLD male sustained trauma in an automobile accident in October, 1967, and three weeks later presented with the chief complaint of shortness of breath. The admission chest film showed nearly complete atelectasis of the left lung (Figure 1). Films at the time of the accident had shown fractures of the left upper ribs, minimal left pneumothorax and some mediastinal air.

What is your diagnosis? (See next page.)

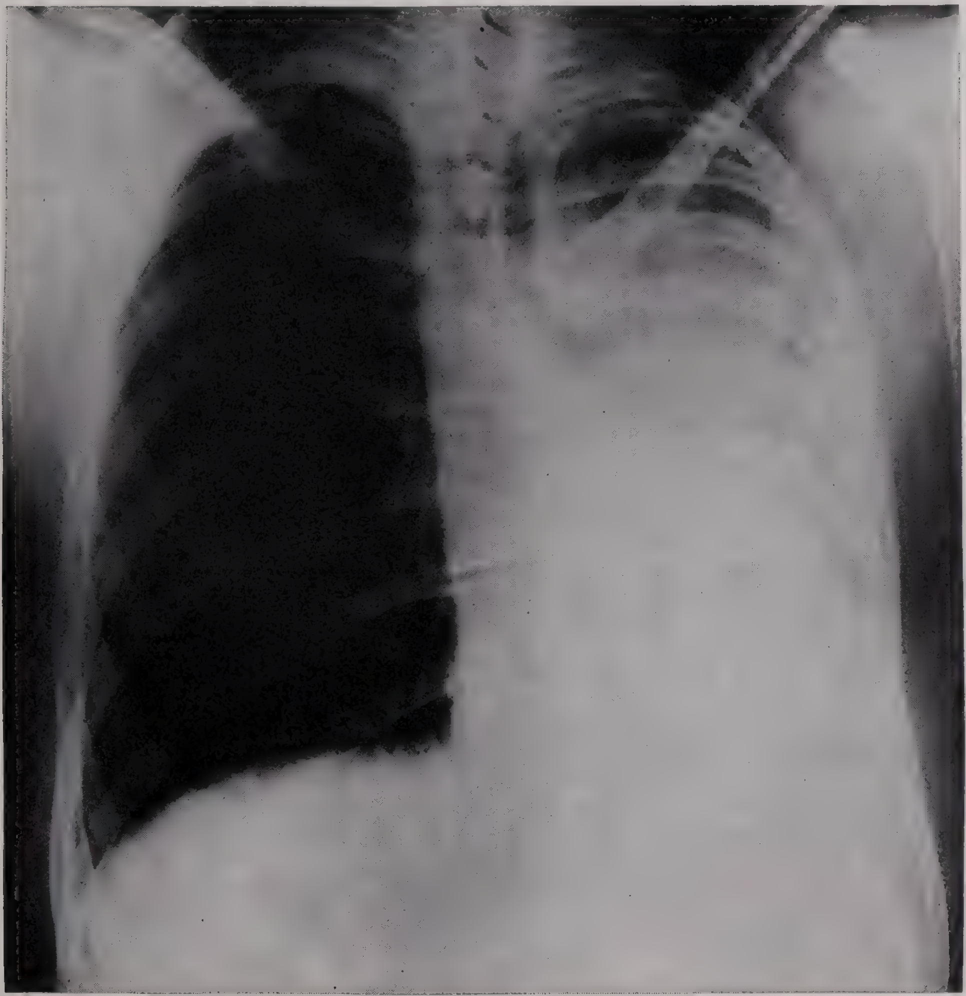

Figure 1

Diagnosis: Rupture of the left main bronchus.

Subsequent planigrams (Figure 2), bronchoscopy and bronchograms (Figure 3) demonstrated a conical occlusion of the left main bronchus, a common sequel to traumatic rupture of the bronchus. Successful surgical repair followed.

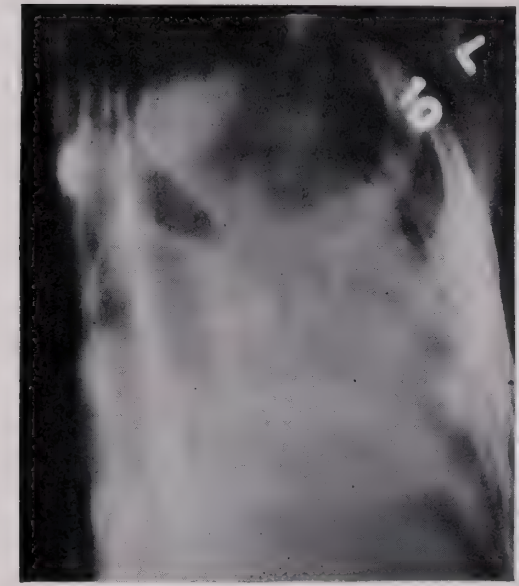

Figure 2

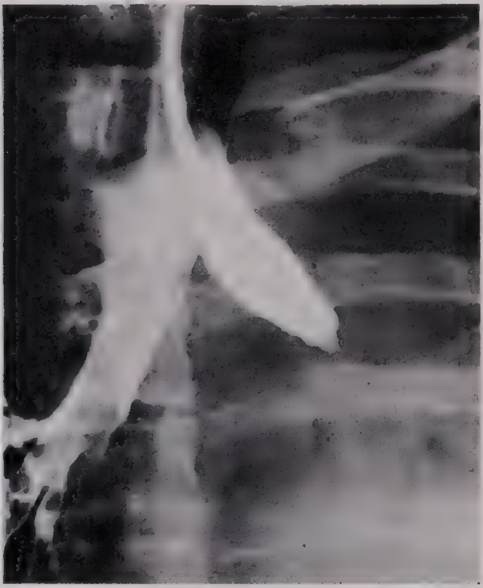

Figure 3

This case clearly demonstrates the need for consideration of possible rupture of the trachea or main bronchus following the ever increasing number of cases of high-impact blunt trauma to the anterior chest wall secondary to vehicular collision. Fractures of the most superior ribs combined with mediastinal air and possibly pneumothorax following anterior chest wall trauma should raise this diagnostic possibility. The effects of bronchial stenosis are usually manifest two to three weeks following the rupture, and if the lumen is completely occluded atelectasis and associated complications will ensue. The narrowing or occlusion is due to the formation of granulation tissue and scarring at the site of the rupture. Prompt diagnosis of traumatic rupture of the trachea or bronchus and subsequent surgical treatment will prevent late complications.

Luther O. Wigdahl, M.D.*
Fridley, Minnesota

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*Department of Radiology, Unity Hospital.

Once there were two brothers. One ran away to sea, the other was elected Vice President, and nothing was ever heard of either of them again.—Thomas R. Marshall

America is not immortal and there are today signs in American life of an alarming deterioration in the things of the spirit.—Cardinal Spellman

Review

Giardia Lamblia as Parasite in Humans

Anton van Leeuwenhoek is credited with the first description of Giardia lamblia in 1681 which he recovered from his own stool.[1,2] It was not until 1859 that Lambl reported it under the name "Cercomonas intestinalis." Finally named in 1915 after Lambl it was placed in the genus Giardia, species lamblia.[3] Giardia possesses a cosmopolitan geographic distribution.[3]

Incidence

Depending on the geographical area as well as the age of the population the incidence varies from 2 to 50%.[2,8,1,7] Infestation is two to three times more common in children who are also more susceptible to its effects.[9,10]

The following three cases will serve to illustrate the clinical symptoms and response to treatment which are fairly characteristic of acute giardiasis.

Characteristics

The trophozoite is rounded anteriorly, tapered posteriorly with a convex dorsal surface, and has a flattened ventral side with a shallow sucking disc near the anterior portion. Four paired flagella arise from superficial organelles on the ventral side. Paired nuclei with single dense nucleoli are readily recognized. Dimensions vary from 9.5 to 21 microns in length, five to 15 microns in width, and 2 to 4 microns in thickness.[4] The trophozoite divides by binary fission.[5]

The cysts appear ovoid or ellipsoidal with a thin, tough wall from which the cytoplasm is characteristically separated. One notes finely granular cytoplasm. Recently formed cysts have two nuclei while the more mature ones have four. The cysts measure 8 to 10 microns in length and 7 to 10 in breadth.[4]

Habitat

The trophozoite characteristically inhabits the duodenum and proximal jejunum where it thrives in an optimum pH of 6.38 to 7.02.[4] Nutrition is felt to be derived from intestinal contents and mucous secretions, although it has been postulated that the trophozoite may feed through attachment of the sucking disc to the microvilli.[3] Zancheck[6] suggested the need for this intimacy with microvilli because he did not find mitochondria or endoplasmic reticulum in the cytoplasm of Giardia lamblia. A carbohydrate rich diet favors the growth of the trophozoite.[3] The attachment to the intestinal mucosa via the sucking disc normally suffices to resist peristalsis. The organism appears to derive random movement through the whipping of the flagella. The cysts are very sensitive to desiccation and are killed at 50°C., but they can survive outside the human body for up to a month.[1,3]

Encystment

Encystment provides for protection and reproduction of the organism.[3] As the trophozoite moves down the intestine it transforms into the cyst.[5] Frankly diarrheal stools yield the trophozoite but encystment occurs more commonly as the liquid stool becomes dehydrated during colonic transit.

Transmission

The cyst usually is transmitted via food and water which has been contaminated with feces through sewage, food handlers, and rarely flies. Man is the natural host and reservoir for Giardia lamblia. Although infestation is more common in children, adults act more frequently as carriers because they are usually asymptomatic.[3] The cyst must be ingested and pass through the stomach before completing its cycle in the duodenum. Transmission requires intimate contact.

Case Reports

Case 1

A 42-year-old white male was admitted to Minneapolis

Veterans Administration Hospital complaining of vomiting, epigastric pain, and mucoid diarrhea. Nine months previously he had been treated for hemorrhagic gastritis but had recurring symptoms since. Three weeks prior to admission the patient had received antibiotics for an episode of pleuritic pain, and subsequently he noted an increase in diarrheal stools from 15 to 20 per day. His alcohol intake had been rather heavy.

Physical Examination

Malnourished, dehydrated, acutely ill. Temperature 101°, epigastric tenderness and RLQ tenderness on rectal examination.

Laboratory

Urinalysis, electrolytes, cephalin flocculation, alkaline phosphatase, fasting blood sugar, and serum bilirubin were normal. Hemoglobin 14 gm/100 ml, WBC 26,000 with left shift. Sedimentation rate 34. BSP retention 22%. Stool and gastric aspirates were guaiac positive. Repeated stool cultures were negative. Barium enema and oral cholecystogram were not remarkable. Roentgenogram of the upper intestinal tract showed a deformed duodenal bulb.

Hospital Course

Intravenous fluids, as well as penicillin and chloromycetin were administered for 15 days. He continued to have mild diarrhea, low grade temperature, and severe headaches. Stool preparations revealed numerous Giardia lamblia. Chloroquine produced no change in symptoms or the parasite. Atabrine produced remission of symptoms and eliminated Giardia lamblia from the stool. The stool remained negative for a nine-month period of follow-up.

Case 2

A 45-year-old white male entered Minneapolis Veterans Administration Hospital with a 12-day history of fever and profuse watery diarrhea (10-12 stools per day). The patient had been treated with Kaopectate and antibiotics by his private physician, but no improvement followed. The patient had lost 10 pounds. He had consumed well water four days before the onset of symptoms.

Physical Examination

Temperature 98.6°, blood pressure 180/80, pulse 72. No acute distress. Diffuse mild tenderness over epigastrum.

Laboratory

Hemoglobin 15.9 gm/100 ml, WBC 9,750/cumm with 80% PMN's, sedimentation rate 18 mm/hr, BUN, FBS, PBI, febrile agglutinins and stool cultures were negative as was the roentgenologic examination of the entire intestinal tract. Giardia lamblia was found in great numbers on stool preparation.

Hospital Course

Atabrine 0.1 gm t.i.d. for five days was followed by complete remission of the symptoms within 72 hours. Follow-up stool examinations were negative.

Case 3

A 24-year-old white male was admitted to Minneapolis Veterans Administration Hospital with a five-week history of up to 10 brown, foul smelling watery stools per day. One month prior to admission, he had returned from Naval duty in Vietnam and the Philippines. He had noted a 35-pound weight loss over a five to six month period, a sensation of "bloating" and cramps which were relieved by expulsion of gas and diarrheal stool, and occasional nausea. The patient associated the onset of symptoms with a visit to Tiajuana, Mexico.

Physical examination was unremarkable.

Laboratory

Hematologic and chemical studies yielded normal results. Roentgenograms of the upper intestinal tract showed an irritable duodenal bulb. Carotene absorption was abnormally low, 57-55 mcg%. Many Giardia lamblia were seen on stool preparation.

Hospital Course

Atabrine 0.1 gm was administered three times daily for five days. Symptomatic improvement followed within 24-36 hours and follow-up stool preparations were negative.

The Clinical Picture

Giardial infestations fail to present a clear-cut and characteristic clinical picture. Patients who have undergone gastrectomy or are malnourished are known to be more susceptible.

Gastrointestinal Symptoms

Usual symptoms are in their order of frequency-diarrhea, abdominal pain, flatulence, abdominal distention, nutritional disturbances, nervous manifestations, anorexia, nausea, vomiting, achlorhydria and anemia.[3] Children usually have severe diarrhea while adults may have diarrhea alternating with constipation.[10] The diarrhea in adults is described as intermittent liquid or soft stools with flocculi or masses of yellow mucus, usually free of blood.[7] Occuring with variable incidence.[12,8,13] Some investigators report that Giardiasis is related to biliary colic and jaundice.[4,11] This has not been borne out as Giardia have only been rarely found in the gall bladder at the time of cholecystectomy (0.7%) and cholecystitis has never been seen in children who have more frequent and more severe infections.[10]

Asymptomatic Individuals

Stool preparations were reviewed in 3187 American soldiers. Giardia lamblia was found in 6.3% of 269 soldiers who had diarrhea, while 5.4% of all others harbored Giardia. A history of diarrhea was elicited in 5.1% of asymptomatic individuals with giardia, while those with a negative history had 5.6%.[7] This type of data has been used by some to show that Giardial infestation in adults may be asymptomatic, while others use this as evidence that Giardia lamblia is not a pathogen.

Rendtorff[14] infected 40 healthy volunteers with Giardial cysts. "Infection" was established in 15 individuals, of whom nine noted a change in stool pattern. An average of 9.1 days elapsed from ingestion to infection (range of six to 15 days).

There remains considerable controversy in the literature as to whether the pathogenicity of Giardia in man is a confirmed entity.[2] It does appear that a commensal relationship exists[8] but it is generally recognized that Giardia may give rise to moderate or intermittent diarrhea and other digestive symptoms and this might be in direct relation to the number of parasites present in the host.[12] The presence of bacteria and malnutrition may act synergistically with Giardia to enhance its pathogenicity.[9]

Malabsorption

There remains some question as to whether Giardiasis causes malabsorption.[11,15] Malabsorption when present, may be attributable to nonspecific abnormalities in the small bowel secondary to protein malnutrition.[16] This is probably true in adults; however, there appears to be no doubt that it can produce malabsorption in children similar to celiac disease which relents with treatment.[2] Yardley[9] gives several possible causes for malabsorption. Giardia may cause direct injury to the intestinal mucosa or it may set up a mechanical barrier due to the massive numbers of parasites. The parasite may cause irritation of the mucosa or alter intestinal motility. Although jejunal mucosal alterations are seen in some patients they are less severe than those of sprue patients.[6,9] There is some evidence correlating malabsorption and the degree of epithelial damage. It would seem that tissue invasiveness is a factor in pathogenesis. Mild clinical cases yield normal biopsies by light microscopy but are abnormal when viewed under the electron microscope. In severe cases both are abnormal.[9]

Invasion of the parasite into the subepithelial lamina propria and submucosa has been demonstrated. Because there are no demonstrable mitochondria or endoplasmic reticulum it has been stated that the Giardia might be rendered antigenically similar to the host so that no inflammatory reaction may result.[17] Electron microscopic studies by Morecki[18] could not confirm invasion. Although he found some in the mucosal cells he concluded invasion was rare and not related to its pathogenicity.

Brandborg[2] states that Giardia was not detected previously in the mucosa because: (1) the staining characteristics are similar or identical to the surrounding tissue, (2) there may be no inflammatory response, and (3) in randomly sectioned tissue only part of the organism is seen. No Giardia were seen in the mucosa of his adult patients who were asymptomatic while mucosal invasion was demonstrated in all those who had diarrhea. Giardia is therefore a significant pathogen although a simple cause-effect explanation does not entirely account for the variability of the lesions reported.[6]

Laboratory Findings

General laboratory findings are generally not helpful in diagnosis.[11] Giardiasis is not associated with a peripheral eosinophilia. Urticaria which relents following treatment has been reported.[19] An altered immune mechanism could be a significant factor in host susceptibility.[20] Hermans[21] described eight patients with dysgammaglobulinemia (virtual absence of IgA and IgM with a moderate increase in IgG), unusual susceptibility to infections, diarrhea with occasional steatorrhea, Giardia in the stools, and nodular hyperplasia of lymphoid tissue in the small intestine. The dysproteinemia persisted after treatment and he felt that Giardia played an opportunistic role.

Diagnosis is based on the demonstration of the parasite in stool preparations. Cysts may be found in formed or semi-formed stool. The trophozoite may be seen in diarrheal stools or duodenal aspirates.[3] Only rarely are the parasites found in the duodenum and not in the stool.[11] Occasionally they may be demonstrated in biopsy material or stained material from duodenal mucus obtained at the time of biopsy. One should check for a history of travel particularly to regions with unsatisfactory sanitation.[9] The diagnosis is usually made by recognition of the cyst in the stool.[3] It must be remembered that frequently there are other parasites present.[12]

Brumpt showed in 1937 an 80% cure of Giardiasis in animals using 1% acridine dye given orally. Galli-Valerio produced a derivative of acridine called Atabrine which has become the treatment of choice.[10,22] The recommended dosage is 0.1 gm t.i.d. for five days in adults, for children the dose is halved.[4] Atabrine (quinacrine) produces 90% clinical and laboratory cure, while chloroquine has shown only 20 to 80% cures.[3] Atabrine is contraindicated in advanced hepatocellular disease.[1] In resistent cases diiodohydroxyquine has been recommended.[9] Boech[23] showed that on treatment the symptoms relent in less than 48 hours, and he considered this response to be diagnostic. Prevention of infection remains a matter of personal hygiene.[7]

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Man

Those who collect the significant documents of our age should not overlook the form on which Jan Masaryk, the famous Czech leader, applied for permission to enter the United States of America. In the space opposite "Race" he wrote "Human."—Everywoman.

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Clues to PVD

The geriatric smoker

In studies on peripheral vascular disease—a common by-product of the degenerative aging process—considerable attention has focused on the important role of smoking in the progression of the disease. Although it may not be etiologic, smoking is widely recognized as a prominent contributing factor.[1]

Skin blood flow—significant factor in PVD. Cutaneous digital vasoconstriction caused by nicotine has been observed both in normal subjects and in patients with peripheral vascular disorders.[1,2] Among patients with peripheral vascular disease, however, age and the severity of the disease appear to modify the effects of nicotine. For example, in a study of older patients with *marked* peripheral vascular disease,[3] changes induced by smoking were not statistically significant for the group as a whole. This was explained on the basis of decreased skin reactivity. *Smoking is not permissible in any stage of the disease,* since even "... minimal reduction in blood flow in patients with ischemic limbs may produce a further reduction in tissue nutrition, and thus may be another case of the proverbial straw on the camel's back."[3]

In another study of patients with peripheral vascular disease,[4] the investigators stress that decreased skin blood flow during smoking "... is the factor of most importance to the patient with peripheral vascular disease." *While such patients may adjust to the discomfort of vascular insufficiency in skeletal muscle, decreased skin blood flow may often lead to severe symptomatology.*

More and more physicians have adopted the practice of investigating for peripheral vascular disorder when confronted with a geriatric patient who is a habitual smoker. Once a diagnosis is established, therapeutic measures are directed toward increasing the peripheral circulation and appropriate management of the patient's general medical needs. These include the important safeguards of keeping warm and refraining from smoking.

Professional model posed for illustration.

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Indications: Conditions associated with deficient circulation; *e.g.,* peripheral vascular disease, vascular spasm, varicose ulcers, decubital ulcers, chilblains, Meniere's syndrome and vertigo.
Caution: Roche Laboratories endorses caution in the administration of any therapeutic agent to pregnant patients.
Side Effects: Transient flushing, gastric disturbances, minor skin rashes and allergies may occur in some patients, seldom requiring discontinuation of the drug.
Dosage: 1 or 2 Timespan Tablets morning and night.
How Supplied: Timespan Tablets—150 mg nicotinyl alcohol in the form of the tartrate salt, bottles of 50.

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Fracture Conference

Shoulder - Hand Syndrome*

Dr. John C. Ivins:†

This case illustrates a most challenging and frustrating symptom complex—the shoulder-hand syndrome.

Dr. Richard H. Turner:‡

This 46-year-old man was involved in an automobile accident on February 21, 1968. He was the only passenger in a one-car accident that occurred when the tire of his car caught on the brim of a curve, and the car went down a 20-foot embankment. He was thrown around inside the car and ended up on the floor on the right front side. At no time was he unconscious; but he remained in the car, unable to move for 20 or 30 minutes, until someone came by and offered to get him out. But he refused the offer because he believed that his back was broken. Finally he was moved by ambulance to the hospital where x-rays demonstrated fractures of both humeri and the pelvis.

In the emergency room he told the attending physician that he had had a myocardial infarction the previous October and that he was presently taking anticoagulants. His arms were put into bilateral Thomas splints at right angles to his body, and he was placed at bed rest, where he remained for four days, during which time his vital signs stabilized. He received a total of four units of blood. At the end of four days his clinical status was stable, and he was transferred to a second hospital 230 miles away. His arms were taken out of the splints and placed on his lap, and he was put on a stretcher. Films taken at the first hospital show the fracture of the right humerus (Figures A and B).

Dr. Ivins:

The film of the left humerus shows a comminuted closed fracture of the proximal third (Figure C). On the right side, there is a closed fracture through the middle third of the right humerus. We do not have the x-rays of the pelvic fracture, but this fracture was considered minor and of no great concern in the treatment of the patient.

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*Fracture conference held June 3, 1968.

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Dr. Sherwin Goldman:*

For ideal on-the-scene management of a traumatic situation of this kind, I would splint the fracture of each humerus so as to minimize the secondary trauma. These bones should be immobilized so that there is no chance of tearing or laceration of the radial nerve.

Dr. Ivins:

How would you do that?

Dr. Goldman:

Depending on what you have at hand, you could use newspapers, pillows, boards, or anything that was available, or just take a blanket and strap both of his arms to his sides.

Dr. Ivins:

Do you think it is important that whoever does this emergency treatment at the scene of the accident examine the hands and wrists to find out whether there is circulation, motion, and sensation there, or whether there is any injury to the major nerves or vessels?

Dr. Goldman:

If that person was capable of evaluating these factors, it would be fine. Then you would have some idea at the time of what the immediate injury had been. If this could not be evaluated, then just placing the injured person in the best possible position would be desirable.

Dr. Ivins:

Do you think anyone licensed to do this sort of work at the scene of the accident ought to be able to detect loss of function of that kind?

Dr. Goldman:

Well, such a person certainly has had experience feeling pulses, and he can try some simple maneuvers of the hands to determine whether there is nerve damage.

Dr. Ivins:

Let us assume that this man has been adequately handled as far as emergency on-site treatment is concerned and he arrives at the hospital with these fractures.

Dr. Goldman:

When he is admitted, I would determine whether his vital signs were stable. There could be some blood loss, and recognition of pelvic injuries involves knowledge about lacerations of the pelvic vessels. First I would make sure that he has an adequate airway. Then I would make sure that his vital signs are stable. After taking his history, you have to consider his anticoagulant therapy and his cardiovascular status against the possibility of continued leakage from the fracture sites. I might be tempted to stop the use of anticoagulants and measure the prothrombin time and blood counts to make sure that these were normal. Then I would turn my attention to the two fractures

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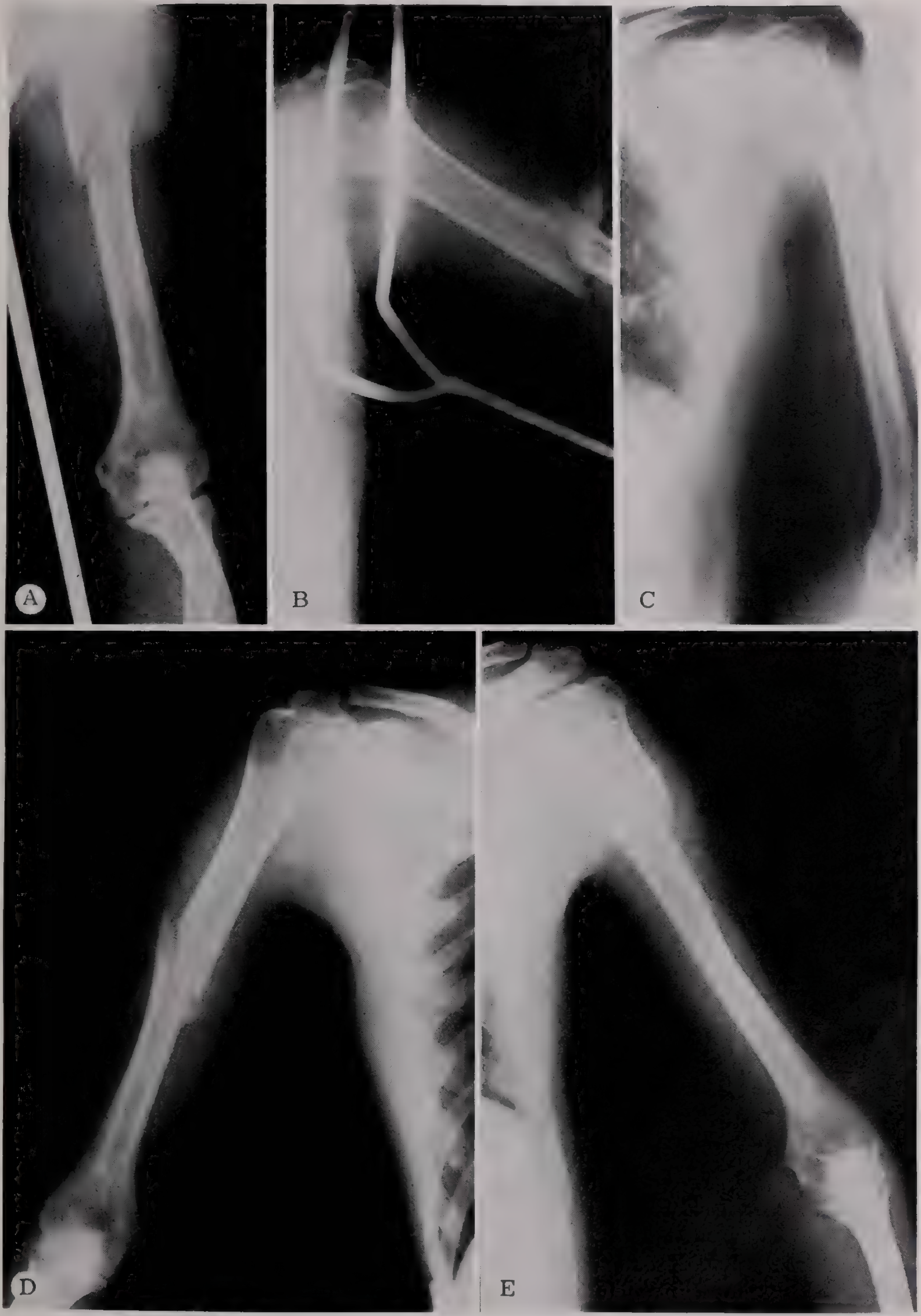

Figure—(A) and (B), Right humerus, February 22, 1968, the day after the accident. Fracture of midshaft of right humerus, with slight displacement. (C), Left shoulder, February 21, 1968, the day of the accident. Comminuted fracture of upper end of shaft of left humerus, with slight angulation. (D) and (E), May 7, 1968, when patient was first admitted to our clinic. Right shoulder (D) seems to be healing. Left shoulder (E).

to make sure that the nerve status was intact.

Dr. Ivins:

For the moment let us forget about the problem of the myocardial infarction and anticoagulants. Just assume the blood count and the prothrombin time are normal. We can then turn our attention to the definitive care of the fractures. Dr. Suiter, how would you treat this fracture problem?

Dr. Ronald D. Suiter:*

The fracture on the right, which is toward the lower end, could be treated by the hanging-arm-cast method. The other fracture, which is a little high, may not be controlled by a hanging-arm cast. I think I would just put the arm with the higher fracture at the patient's side and see what kind of position it holds. If the arm holds its reduction while in this position, I would go ahead and apply a Velpeau dressing on it. If it did not hold then I would try to place it in the abducted position.

Dr. Ivins:

As I said, the pelvic fractures were minor and of no significance. We can, therefore, disregard them. Dr. Suiter, you would put the right side in a hanging cast and immobilize the left side with a plaster cast. Is that right?

Dr. Suiter:

I would use either a plaster or Velpeau dressing, depending on how the arm lined up. I cannot see the fracture too well on the second x-ray (Figure C).

Dr. Ivins:

Dr. Peterson, will you give us your opinion of this problem?

Dr. Hamlet A. Peterson:†

Initially, there was a question of a spinal fracture. Was there in fact a spinal fracture?

Dr. Turner:

The pain that the patient felt was from his pelvic fracture. He only thought he had broken his spinal column.

Dr. Peterson:

Essentially, he has fractures of both arms. I would think that it would be better to get him up into a sitting position and probably put each arm in a hanging cast to see how they line up.

Dr. Turner:

The patient was transferred to the second hospital and was placed in bed with his arms out on two chairs. The next morning bilateral long-arm casts were applied. The right arm was laid across his abdomen and traction applied to the left arm. Attendants put traction to the end of the bed, and the patient remained in bed for four or five weeks because of the pelvic fracture. Of course, he would sit up for a short while at meals, and therefore his pelvic fracture was somewhat affected. About the time the casts were put on, approximately the fifth day after the injury, he noted that he could not use his hands as well as he had previously. By the time the casts were removed, he had essentially no function of the shoulder and the joints of his hands, because of the long-term immobilization. He was given physical therapy, which consisted of heat to the joints of both extremities and passive, somewhat forceful, range-of-motion exercises to the point of discomfort. This physical therapy was carried out for four weeks, during which time there was very little improvement. It was then decided that the therapy could be done at home. After one week at home, because there was not much progress, he decided to come to our clinic. This was 11 weeks after the accident. These are the x-rays that were taken on admission (Figures D and E).

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Dr. Ivins:

This is 11 weeks after the accident. Dr. Santos, what about the state of the fracture?

Dr. Ray E. Santos:*

It appears to be united, although the fracture line still can be seen. Was he having any pain?

Dr. Turner:

On arrival he was having pain with motion of any joint in his upper extremities. He had 20° of abduction in each shoulder, 20° of flexion in his left elbow, and 30° in his right elbow. There was stiffness in all of his fingers—most severe in his right hand—and swelling of both hands. He had some mild hypesthesia in the thumb and index finger distribution in his right hand, and almost a glove hypesthesia in his left.

Dr. Santos:

Was there motion in the fractures? If so, it is not clinically solid.

Dr. Ivins:

How would you determine that?

Dr. Santos:

By manipulation.

Dr. Ivins:

I did that. I took him to the Section of Diagnostic Roentgenology, and by using the image intensifier I attempted to do just that. The scapulas would move a little on the chest wall, but nothing else would move. Neither the fracture nor the shoulder joint moved. I do not know whether I proved anything, and I do not know that the fractures were solid, but at least there was enough fixation so that it was about equal to the fixation of the shoulder joint.

Dr. Santos:

At this point, if the fracture could not be moved under the image intensifier, I would start mobilizing the adjacent joints, beginning with the shoulder and using physical therapy. You could be a little more aggressive with his elbows.

Dr. Turner:

Passive range of motion to the point of pain tolerance was given.

Dr. Santos:

As far as the therapy is concerned I think that would be about as far as

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I would want them to go.

Dr. Ivins:

The point is that the patient had only passive manipulation of his stiff joints, all of which were extremely painful. He had never had active motion exercises. Throughout this time, he had had frequent, passive manipulations of his injured painful joints which grew steadily worse instead of better. Would anybody like to comment on that?

Dr. William H. Bickel:*

Did they ever check the cervical region of his spinal column?

Dr. Ivins:

His cervical spinal column was all right. By this time he had a classic, chronic, bilateral shoulder-hand syndrome, with almost the textbook picture—swollen hands with all the fingers stiff in extension. There was no motion in any joint in either hand except a tiny amount in all fingers except the right index finger, which could not be flexed at all.

Dr. Vu V. Nguyen:†

Since Steinbrocker's[1] first description of the natural history of the shoulder-hand syndrome in 1947, as a specific type of reflex sympathetic dystrophy, there has been voluminous literature reporting various causes and pathophysiologic mechanisms of this condition which has been described under many different names: shoulder-arm syndrome, posttraumatic dystrophy, posttraumatic spreading neuralgia, and neurotrophic rheumatism (in Europe exclusively).

Etiology

The exact cause of the shoulder-hand syndrome has not been satisfactorily determined. It has been postulated that afferent stimuli from trauma to the upper extremity, from trauma to the heart (myocardial infarction), or from trauma to the central nervous system (stroke or brain tumor) cause widespread disturbances of sympathetic centers in the cervical cord. These disturbances increase sympathetic outflow and cause pathologic changes in the extremity involved. In turn, these changes result in pain, which acts as a feedback system to perpetuate the sympathetic outflow.

If this outflow can be blocked or modified long enough to allow reversal of the disease, the vicious cycle can be broken and the patient will recover. The sympathetic overactivity provokes continuous vasospasm of the terminal arterial channels. Capillaries and venules become distended with sluggishly flowing blood lacking the propulsive pressure transmitted from the arterioles. This is the basis for the cyanosis and coldness of the hand. Slowly moving blood develops a low pH, which promotes dissolution of mineral salts from bone. Arteriolar spasm effects a relative ischemia of all tissues. As a consequence, increased permeability of capillaries and venules permits diffusion of plasma and its fibrin content into the tissue spaces, manifested clinically as edema. Fibrin deposition is followed by fibrosis replacement, which accounts for the thickening of the palm. In addition, the mobility of joints is restricted and never fully recovered. An accurate diagnosis can be made in a high percentage of cases by application of the criteria enumerated by Steinbrocker[1] in his original paper.

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Course

The course of the disease is divided into three stages[2] of from three to six months each, though the entire course may be telescoped into a matter of a few weeks.

In the first stage, the shoulder has various degrees of pain, with restriction in all ranges of motion, especially in abduction and external rotation. The hand is swollen, with thickened palmar fascia and cutaneous hypesthesia. Vasomotor instability is manifested by a purplish, reddish mottling of the skin. The fingers have thickening of the dermis and are held in moderate flexion, with severe increase in pain on attempts to further flex or extend them.

In the second stage, there is increased tightness of the shoulder, with possible atrophy of the muscles. Roentgenograms may show patchy osteoporosis of the head of the humerus and early osteoporosis of the wrist and fingers. Edema is decreased in the skin, which is shiny and dystrophic with obliteration of the skin creases in the hand (sclerodactylic type).

In the third stage, which may last for years, there is dissipation of pain in both the hand and the shoulder, with residual contracture. The contracture of the fingers can be so severe that the extremity may be completely useless.

Treatment

Treatment must be psychologic and physiologic. Patients with the shoulder-hand syndrome usually are very distressed and in need of sympathy. The physiologic treatment must aim at blocking the sympathetic overactivity and correcting the consequences of the sympathetic dystrophy (pain, stiffness, osteoporosis). The patient must be given adequate analgesic medication combined with physical therapy of the extremity involved (range of motion exercise, active exercises with stretching of shoulder in abduction, dynamic splinting of the fingers). Some authors advise heat, massage, and local injection of cortisol (compound F). Cortisone can be given during a period of 10 days. Blocking of the sympathetic outflow to the extremity can be realized by different sympatholytic medications or by local blocking of the stellate ganglion with an anesthetic agent.

When the symptoms of the shoulder-hand syndrome are severe or chronic, sympathetic denervation of the upper extremity may be indicated. In 1922, Bruning[3] reported that excision of the stellate ganglion was more effective than periarterial sympathectomy. Complications after stellectomy* include Horner's syndrome, which may be transient or permanent. Thus, to avoid this complication, sympathetic denervation has been extended progressively to removal of the first three thoracic ganglions, especially T-2. Approach to these ganglions can be made anteriorly, posteriorly, transpleurally, or extrapleurally. In 1954, Atkins[4] credited Goetz and Schulze of Cape Town, South Africa, with being the first to use the transaxillary approach to cervicothoracic sympathectomy.

Dr. Ivins:

I feel that there was a clear indication in this situation to do an open reduction on the right side. I think that arm would have been functionally normal. I say that without knowledge about the index finger. As Dr. Turner pointed out, the patient had some hypesthesia on the dorsum of his first web space on the index finger and the dorsum of his thumb. If this had been recognized at the time, I would have been more in favor of doing an open reduction. I would like to have some comment on this. Do you think the index finger is related in any way to median nerve injury at the fracture site?

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* See Test Your Word Score Page 1087.

Dr. Edward D. Henderson:*

I do not see how. I do not know why the index finger on the right was so much more severely involved. And I do not see how you can injure the median nerve that high without having more evidence.

Dr. Ivins:

Any other comments or questions about the shoulder-hand syndrome as illustrated in this case?

Dr. Henderson:

Have your patients been relieved by the drugs that are supposed to block the sympathetics?

Dr. Ivins:

I have never used any of those drugs. The only other approach to this problem in my experience was some years ago when we used to give steroids orally. But I was never as impressed with that program as with a skillfully performed stellate ganglion block.

John C. Ivins, M.D.†
Vu V. Nguyen, M.D.†
Einer W. Johnson, Jr., M.D.†
Rochester, Minnesota

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†From the Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

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Walk of Life

"Exercise," the doctor said,
"I certainly suggest.
And studies in the field of medicine say walking's best.

"It helps the breathing, helps the heart,
Improves the muscle tone.
And now excuse me, must depart."
And he hung up the phone.

And walked, yes walked and walked, it's true,
With healthful stride. How far?
From where he had been sitting to his car.

—Richard Armour: The Medical Muse, 1963.

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Long recognized for its usefulness in the treatment of moderate to severe anxiety, Mellaril is now also known to be effective against mixed anxiety-depression.

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Contraindications: Severe central nervous system depression, comatose states from any cause, hypertensive or hypotensive heart disease of extreme degree.
Warnings: Administer cautiously to patients who have previously exhibited a hypersensitivity reaction (e.g., blood dyscrasias, jaundice) to phenothiazines. Phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides. During pregnancy, administer only when necessary.
Precautions: There have been infrequent reports of leukopenia and/or agranulocytosis and convulsive seizures. In epileptic patients, anticonvulsant medication should also be maintained. Pigmentary retinopathy may be avoided by remaining within the recommended limits of dosage. Administer cautiously to patients participating in activities requiring complete mental alertness (e.g., driving). Orthostatic hypotension is more common in females than in males. Do not use epinephrine in treating drug-induced hypotension. Daily doses in excess of 300 mg. should be used only in severe neuropsychiatric conditions.
Adverse Reactions: *Central Nervous System*—Drowsiness, especially with large doses, early in treatment; infrequently, pseudoparkinsonism and other extrapyramidal symptoms; nocturnal confusion, hyperactivity, lethargy, psychotic reactions, restlessness, and headache. *Autonomic Nervous System*—Dryness of mouth, blurred vision, constipation, nausea, vomiting, diarrhea, nasal stuffiness, and pallor. *Endocrine System*—Galactorrhea, breast engorgement, amenorrhea, inhibition of ejaculation, and peripheral edema. *Skin*—Dermatitis and skin eruptions of the urticarial type, photosensitivity. *Cardiovascular System*—Changes in the terminal portion of the electrocardiogram have been observed in some patients receiving the phenothiazine tranquilizers, including Mellaril (thioridazine hydrochloride). While there is no evidence at present that these changes are in any way precursors of any significant disturbance of cardiac rhythm, several sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients previously showing electrocardiographic changes. The use of periodic electrocardiograms has been proposed but would appear to be of questionable value as a predictive device. *Other*—A single case described as parotid swelling.

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Warning: In renal impairment, since liver toxicity is possible, lower doses are indicated; during prolonged therapy consider serum level determinations. Photodynamic reaction to sunlight may occur in hypersensitive persons. Photosensitive individuals should avoid exposure; discontinue treatment if skin discomfort occurs.

Precautions: Drowsiness, anorexia, slight gastric distress can occur. In excessive drowsiness, consider longer dosage intervals. Persons on full dosage should not operate vehicles. Nonsusceptible organisms may overgrow; treat superinfection appropriately. Treat beta-hemolytic streptococcal infections at least 10 days to help prevent rheumatic fever or acute glomerulonephritis. Tetracycline may form a stable calcium complex in bone-forming tissue and may cause dental staining during tooth development (last half of pregnancy, neonatal period, infancy, early childhood).

Adverse Reactions: *Gastrointestinal*—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. *Skin*—maculopapular and erythematous rashes; exfoliative dermatitis; photosensitivity; onycholysis, nail discoloration. *Kidney*—dose-related rise in BUN. *Hypersensitivity* reactions—urticaria, angioneurotic edema, anaphylaxis. *Intracranial*—bulging fontanels in young infants. *Teeth*—yellow-brown staining; enamel hypoplasia. *Blood*—anemia, thrombocytopenic purpura, neutropenia, eosinophilia. *Liver*—cholestasis at high dosage.

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Otolaryngology Clinics

The Diagnostic Management of the Neck Mass*

THE HEAD AND NECK are most accessible for examination with little discomfort to the patient. By utilizing a few basic principles, the physician may quickly arrive at the best diagnostic probabilities in a patient with a neck mass.

The history is the first clue to diagnosis. Previous operations should be documented. To be considered in cervical swellings are the growth pattern, the presence of pain or hoarseness, neurological deficit, and concomitant systemic illness. Taking the history should include inquiries into problems of dysphagia, nasal obstruction or drainage, diplopia, hearing loss and tinnitus. The method and duration of alcohol and tobacco use are pertinent, because oropharyngeal malignancy is prevalent in the "straight-shot artist" and laryngeal carcinoma in the smoker.

Suppuration and hemorrhage can cause rapid changes in a neck mass and may obscure the diagnosis. A painless, enlarging mass suggests malignancy in any age group. Intermittent swelling related to eating over a period of time indicates benign salivary gland disease. Size change related to increased intrapharyngeal pressure should be sought; this suggests laryngocele. Vascular aneurysms pulsate, while fluctuation suggests a cystic structure such as a lymphangioma or branchial cyst.

Infant and Childhood Neck Masses

Lymphadenitis is by far the most common cause of childhood neck masses. A careful examination will reveal palpable nodes bilaterally. Such swellings are commonly related to an upper respiratory infection; they rarely warrant operative intervention. A diagnostic challenge presents when nodes coalesce or when drainage develops. Atypical acid-fast bacteria, dermatitis, and parasitic scalp infestations have recently become mounting considerations. Sarcoidosis and tuberculosis are less common. Viral disorders such as infectious mononucleosis and cat scratch fever are characterized by general lymphadenopathy. Dental infections and pharyngeal space infections are to be considered in toxic children. Less common causes of cervical swelling include cystic hygroma,† branchial cleft anomalies and dermoids.

Midline neck masses are almost invariably thyroglossal duct cysts. This is the rationale behind the old adage that midline masses are benign, whereas lateral masses may be malignant. Occasionally a dermoid will present in the midline.

Although a malignant process in a child's neck is very uncommon, occasionally a lymphoma will be encountered. A single, enlarging mass is indicative of sarcoma, while several adjacent, unilateral nodes suggest Hodgkin's disease.

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†See Test Your Word Score Page 1087.

Adult Neck Lumps

In normal adults, it is often possible to palpate cervical lymph nodes. Some may be as large as 1.0 to 1.5 cm, particularly in the subdigastric or submaxillary area.

In the adult, malignancy is the major consideration, while many swellings will prove to be benign. Lymphoma is probably the most common cause of a malignant neck mass in the young adult and usually represents a local sign of a generalized disease. Inflammatory and congenital neck masses, neurofibromas, lipomas, and carotid body tumors are less commonly encountered.

Geriatric Neck Masses

Here the overwhelming consideration is metastatic malignancy; over 80 percent of the masses will prove to be malignant. Unfortunately this adage is becoming increasingly true also for middle-aged and even young adults. Occasionally the primary lesion will be located below the clavicle, but this is the exception. Most are in the oral cavity, pharynx, or larynx, and it is incumbent upon the physician to investigate these areas thoroughly. Benign salivary gland neoplasms or duct obstruction, branchial cleft anomalies, carotid body tumors, and lymphomas will be less commonly encountered.

The Diagnostic Approach

After historical data has been tabulated, the office evaluation of a cervical mass should include an inspection of the neck from the front and palpation from behind. The sternocleidomastoid muscle is the key to the lateral neck. Neck flexion against resistance brings the muscle out, making it easier to define its relationship to an adjacent mass. Relaxing the muscle by tilting the head will allow the physician to palpate the ipsilateral neck.

The major cartilages of the neck should be delineated. The hyoid bone and the transverse processes of the cervical vertebra can be palpated. The lateral lobes of the thyroid should also be carefully palpated. Swallowing will move the thyroid gland over a gently applied palpating finger, allowing delineation of small nodules. A rough sketch of the neck serves as a graphic recording for physical findings (Figure 1).

The skin of the face and scalp should be carefully searched. A thorough ear, nose and throat examination is essential (Figure 2). Emphasis should be placed on the nasopharynx, nasal fossa and the base of the tongue. Unsuccessful mirror laryngopharyngoscopy or nasopharyngoscopy necessitates a more formal examination. Palpation is an often neglected but extremely important adjunct to the general otolaryngological examination. The palpating finger is a useful instrument for detection of small lesions in the posterior third of the tongue; oral and upper neck masses can be delineated by bimanual palpation. These procedures will often yield an otherwise occult malignancy. A funduscopic examination is particularly indicated where a melanoma is a possibility. Evaluation of the cranial nerves is equally necessary. A bruit suggests narrowing of the carotid system; a mass at the carotid bifurcation that is mobile laterally but not up and down suggests a carotid body tumor. Diagnosis and extent can be established by angiography. A chest x-ray is imperative. Routine blood studies and skin tests help define systemic and infectious disorders.

There will be occasions when a suspected primary will not be apparent despite meticulous inspection and biopsy. The importance of the general physical examination and a detailed review of systems cannot be overemphasized. Before resorting to an open biopsy, esophagoscopy, bronchoscopy and nasopharyngoscopy, sinus films, and excretory urography are indicated. Oral staining is gaining acceptance where a leukoplakia is widespread. Salivary gland and thyroid scanning is useful. Sialography, angiography, and venograms are necessary in special cases.

Biopsy of the nasopharynx is especially indicated where nodes deep to the upper sternocleidomastoid muscle or in the posterior triangle are encountered. Normal mirror nasopharyngoscopy does not eliminate the possibility of a nasopharyngeal primary neoplasm. Base of tongue and lingual tonsil biopsy may yield positive results. Diagnostic tonsillectomy has been done where initial biopsies could not document a suspected malignancy. There will be rare occasions when all investigation fails to identify a source for a neck mass. One is seldom justified in observing a neck mass in an adult. As a last resort, tissue must be obtained for pathological study.

A controversy is still current regarding the merits of needle versus open biopsy. If an open biopsy is indicated, the incision must be in a position where the local area can be excised if a larger operation is necessary. A needle biopsy site should be similarly placed and tattooed for later identification and excision. While frozen sections are increasingly reliable, there will be times when permanent sections will be required for diagnosis. An individual's experience, the mass, and the general status of the patient should be considered before securing tissue for pathological examination.

Case Report

A 59-year-old street maintenance worker was referred for diagnosis and treatment after excisional biopsy of a right neck mass, 4 x 2.5 x 1.8 cm and pathologically a poorly differentiated squamous cell carcinoma. One month prior to admission he had noted a single, painless, enlarging mass in the right lateral neck. He denied hoarseness, dysphagia, sore throat and voice change. Although he had smoked one to two packs of cigarettes daily for 40 years, this had recently been reduced. He was a heavy drinker. Following referral, an indirect mirror laryngoscopy was done. This revealed a 2-cm mass in the right pyriform sinus with normal vocal cord mobility. Biopsy of the lesion via direct laryngoscopy showed the same histology as the neck mass. The patient is now undergoing a course of preoperative irradiation to be followed by a lateral pharyngectomy and ipsilateral neck dissection.

Comment

Excision of the neck mass served only to delay definitive diagnosis and possibly contaminate the neck. The proper diagnostic approach would have been to tentatively assume (in this case correctly) that the neck mass was a metastasis and then search for the primary lesion.

Summary

The generalist, the dentist, and the specialist all have responsibility in the diagnosis of neck masses. An approach has been outlined which will avoid delays in diagnosis. Occasionally, biopsy of the neck mass is necessary, but usually the pathology of such a mass is best discovered by location of the primary tumor elsewhere in the head and neck without neck biopsy. In cases of malignancy, it is of extreme importance to preserve the integrity of metastatic neck nodes to prevent seeding of malignant cells.

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Laboratory Letter

A Little on Lupus and Its Fluorescent Nucleus

Have you ever had problems establishing a diagnosis of systemic lupus? Chances are, you have. For good reasons, too. Clinically, the disease can attack any organ; tends to wax and wane; mimics related disorders, such as rheumatoid arthritis and other connective tissue diseases; and, more often than not, fails to give the textbook picture of a young woman with a butterfly rash, joint pains, sensitivity to sunlight, and leukopenia. Furthermore, even confirmed cases may have negative LE preparations; corticosteroids may suppress formation of LE cells; and many drugs can cause positive tests for lupus (Table 1).

TABLE 1

Drugs That Occasionally Give Positive LE Tests

Aminosalycylic Acid
Diphenylhydantoin
Griseofulvin
Hydralazine
Isoniazid
Mophenytoin
Methylthiouracil
Methyldopa
Oral Contraceptives
Penicillin
Phenylbutazone
Procainamide
Propylthiouracil
Streptomycin
Sulfadimethoxine
Sulfamethoxypyridazine
Tetracyclines
Trimethadione

To render precise diagnosis even tougher, tests that directly or indirectly signal the presence of lupus may cross react with serum factors generated by other diseases (Table 2).

TABLE 2

Percent of Abnormal Tests in Lupus and Related Diseases

				Connective Tissue Diseases			
Test	Adult Rheumatoid Arthritis	Juvenile Rheumatoid Arthritis	Ankylosing Spondylitis	SLE	Dermatomyositis	Periarteritis Nodosa	Scleroderma
LE cell	15%+	Rare	Negative	50-75%	Negative	Negative	Negative
Fluorescent Antinuclear antibody, titer 1:8	35%+	20%+	Negative	95-100%	10%+	10%+	70%+
Rheumatoid factor, titer 1:80	70%+	15%+	Negative	25%+	10%+	25%+	33%+

What is the fluorescent antinuclear antibody test, or FANA? In our hands, it consists of dropping fluorescein-labeled anti-human gamma globulin on an imprint of human spleen overlaid with a patient's serum. If the antibody reacts with antigen, the resulting complex fluoresces and the test is positive. We can see the nucleus glitter through an ultraviolet light microscope.

How do you interpret the result? First, FANA tests are positive in almost all patients with systemic lupus, even when LE tests are negative. Yet related diseases, especially scleroderma, can give rise to fluorescence. Still, and here lies the greatest value of FANA, a negative test virtually excludes systemic lupus. In short, all that glitters is not lupus, but lupus almost always glitters.

Richard L. Reece, M.D.
Minneapolis, Minnesota

References may be secured from the author.

Drugs

Ethchlorvynol (Placidyl)

Addiction Hazard

Floyd D. Garetz, M.D.*
Minneapolis, Minnesota

It is the purpose of this paper to bring into focus what appears to the author to be the serious addiction hazard of ethchlorvynol (Placidyl). Ethchlorvynol was introduced to the North American continent in 1955 and has been used as an agent for day-time tranquilization as well as for night-time sedation. Many patients report that it produces a feeling of euphoria; most find that it relieves anxiety and is a useful sleeping medication.

As with many synthetic sedative and tranquilizing agents, ethchlorvynol was thought at first to be non-addicting. However, as with most drugs classified as minor tranquilizers as well as those called non-barbituric hypnotics, cases of addiction began to appear in the literature approximately five years after introduction of the drug. In a recent review article. Essig[1] summarizes reports of addiction to seven of the minor tranquilizers or non-barbituric hypnotics as follows: meprobamate (Equanil or Miltown); ethchlorvynol (Placidyl); glutethimide (Doriden); ethinamate (Valmid); chlordiazepoxide (Librium); diazepam (Valium); and methyprylon (Noludar).

Case Report†

The patient, a thirty-year-old male, was admitted to the hospital on September 27, 1968. On September 24 he had first revealed to his psychotherapist that he had been taking ethchlorvynol in amounts of 1500 to 2000 mgm. a day over a period of one and a half to two years but that he had stopped taking it on September 17. He reported that he had continued to take ethinamate (Valmid) during the week of September 17 to 24.

On September 26 the patient was noted to be confused at his place of work and to act as if he were hallucinating. Upon admission to the hospital on September 27, he was actively hallucinating and showed a typical picture of delirium. There were no convulsions.

Except for a hypertension of 164/100, physical and neurologic examinations were normal. Fasting blood sugar was slightly elevated to 100 mgm.% but blood urea nitrogen, cholesterol, A/G ratio, protein-bound iodine, alkaline phosphatase serology, hemogram and urinalysis were normal.

The patient was treated with thioridazine (Mellaril) and promazine (Sparine); no anticonvulsant medication was employed. He showed progressive improvement to complete clearing of consciousness on October 2 and was discharged from the hospital on October 3.

The case reported in this paper is similar to other cases reported in the literature. A review of the English literature for reports of addiction to ethchlorvynol has yielded a total of 11 cases.

The Table is a summary of certain features of 10 of the reported cases of ethchlorvynol addiction.

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*Associate Professor, Department of Psychiatry, University of Minnesota Medical School, Minneapolis.
The author wishes to express his gratitude to S. W. Shapiro, M.D., and to S. J. Zak, M.D., for their help in preparing this paper.

Clinical Picture

On the basis of the cases presented in Table I the following points should be noted:

1. Addiction to ethchlorvynol appears in both sexes and in a wide range of ages.
2. Convulsions occur in a large proportion of cases along with a typical picture of delirium much like the delirium tremors seen in withdrawal from alcohol.
3. Clearing of symptoms occurs in five to 12 days.
4. Addiction can occur in amounts as low as 1250 mgm. per day and after only a few months of usage.
5. The cases reported were not sufficiently clear on the matter of lag period between stopping the drug and onset of symptoms. However, a lag period of from two to seven days is likely.

Treatment

A major problem in treatment is that a patient may not be suspected of being addicted to ethchlorvynol. The patient is admitted to a hospital for other purposes and, because of forced withdrawal from the drug, exhibits delirium and/or convulsions unexpectedly.

The following are guide lines in treating the withdrawal state:

1. Hospitalization is required.
2. Careful observation of food and fluid intake and output is necessary. Appropriate supportive measures should be taken when voluntary intake is not adequate.
3. Seizure precautions should be taken.
4. Phenothiazine compounds should be used to control the psychosis and agitation.

TABLE

A Summary of 10 Reported Cases of Ethchlorvynol Addiction

Case Reporter	Sex	Age	Symptoms	Symptoms Cleared	Dosage/Daily	Duration
Garza[2]	Male	40	Delirium Hallucinations Convulsions	5 days	4000 mgm.	10 years
Garza[2]	Female	26	Delirium	10 days	1000-2000 mgm.	7 years
Blumenthal[3]	Male	47	Hallucinations Convulsions	10 days	2000-2500 mgm.	9 months
Wood[4]	Female	66	Hallucinations Convulsions	12 days	2000-3000 mgm.	6 months
Hudson[5]	Female	40	Delirium Hallucinations Convulsions	10 days	1500 mgm.	Several months
Aycrigg[6]	Female	38	Delirium Hallucinations	6 days	500-2000 mgm.	1 year
Aycrigg[6]	Male	39	Delirium Hallucinations Convulsions	7 days	1000-2000 mgm.	2 years
Abuzahra[7]	Male	67	Delirium Convulsions	11 days	1250 mgm.	5 months
Cahn[8]	Female	35	Hallucinations Convulsions	?	2500 mgm.	2 years
Cahn[8]	Female	36	Convulsions	?	2000-3000 mgm.	7 months

5. Anticonvulsants should be used to reduce probability of convulsions.
6. Ethchlorvynol can be given in amounts taken by the patient before withdrawal with gradual reduction over a period of one week.
7. Phenothiazine and anticonvulsants should be continued for two weeks.

Summary and Conclusions

Ethchlorvynol (Placidyl) is a sedative, tranquilizing drug with a serious addiction hazard. Its effect of euphoria and the very narrow margin between therapeutic dosage and addicting dosage make it an even greater addiction liability than other drugs in its class.

The therapeutic use of ethchlorvynol should be restricted to hospital patients.

Patients suspected of being addicted to ethchlorvynol should be hospitalized and treated with gradual reduction of the drug as well as with phenothiazines, anticonvulsants and general supportive measures.

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Medical Reporting

An all-too-common disease of early miners was silicosis. This was particularly true in the Rockies, where tunnels were forced through the mountains to get at gold deposits. Hard-rock miners at Central City, Colorado, died at an average thirty-eight years of age. Dr. H. A. Lemen of Denver described such a sufferer, whose health failed while working on a mining tunnel in Jones Mountain. He was emaciated, coughed and sweated a great deal at night, and ran a temperature of 103 degrees.

"He was expectorating daily large quantities of fluid, a specimen of which I exhibit you in this bottle," said the doctor, addressing the infant Colorado Medical Society. "He not infrequently expectorated a pint and a half to two pints of this fluid in 24 hours. His pillow case and shirt bosom were bespattered with what looked like black ink. The sentence that I am now reading was written with this fluid. The pen used has never been in ink."*

---

*Richard Dunlop: Doctors of the American Frontier, 1965.

Grass

Grass is the forgiveness of nature—her constant benediction. Forests decay, harvests perish, flowers vanish, but grass is immortal.—Ingalls

Meetings

Neural-Science Seminar

A Seminar in Neurology, Neuroradiology and Neurosurgery will be held at the Minneapolis Veterans Administration Hospital on August 6, 7, and 8th. Recent advances in these fields will be reviewed. Physicians and other medical personnel are invited to attend. Cost of the Seminar will be borne by the Veterans Administration Hospital, Minneapolis, Minnesota. Rooms have been reserved for visiting participants at a minimal cost at the Sheraton Motor Inn on Highway 494. A social program as well as the lectures by outstanding faculty is being planned. You may register by writing to Dr. Milton Alter, Chief of Neurology Service, Veterans Administration Hospital, Minneapolis, Minnesota.

Southern Minnesota Medical Association Meeting

Annual convention for Southern Minnesota Medical Association in Minnesota Medicine, Saturday, September 13, 1969 at the Inn Towne Motel in Albert Lea, Minnesota.

Dermal Pathology

The University of Minnesota will present a five day course in Dermal Pathology on August 18-22, 1969. This is specifically directed to dermatologists and pathologists and will provide a very comprehensive review of the basic concepts of dermal pathology. For further information contact: Lee D. Stauffer, College of Medical Sciences, Box 193 Mayo Building, University of Minnesota, Minneapolis 55455.

Diabetes Detection

The Diabetes Detection and Education Center has been established to provide physicians in this region with a comprehensive and efficient patient and family educational program. The purpose of the Center is to serve as a resource for the physician. Patients are accepted by referral and are returned to their personal physician's care at the end of the five-day course. A complete summary of the patient's progress and acceptance of his disease is sent to each physician along with the results of all laboratory data, diet schedules, and diapeutic regimes. Five-day courses are available for patients every other week. Starting dates of these are listed below. The patient may commute from the home, community hospital, or from nearby motels or hotels. A minimal tuition is charged for the 40-hour course which includes the cost of patient's meals, laboratory determinations, insulin, etc. Patients may be enrolled by writing the Diabetes Detection and Education Center at 916 East 15th Street, Minneapolis, Minnesota 55404, or by calling 332-2446.

1969 CLASSES ARE SCHEDULED FOR THE WEEKS OF:

July 21
August 4
August 25
September 8
September 22
October 6
October 20
November 3
November 17
December 1
December 15

The burdened heart...

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tigue, depressive symptoms or
itation; acute agitation, tremor,
lirium tremens and hallucinosis
ie to acute alcohol withdrawal;
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sociated with temporary increase
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eous ingestion of alcohol and other
NS depressants. Withdrawal
mptoms have occurred following
rupt discontinuance. Keep addic-
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irveillance because of their pre-
sposition to habituation and
ependence. In pregnancy, lactation
women of childbearing age, weigh
otential benefit against possible
azard.

recautions: If combined with other
ychotropics or anticonvulsants,
nsider carefully pharmacology of
gents employed. Usual precautions
dicated in patients severely de-
ressed, or with latent depression, or
ith suicidal tendencies. Observe
sual precautions in impaired renal
hepatic function. Limit dosage to
nallest effective amount in elderly
nd debilitated to preclude ataxia
oversedation.

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plopia, hypotension, changes in
bido, nausea, fatigue, depression,
ysarthria, jaundice, skin rash,
axia, constipation, headache, in-
ntinence, changes in salivation,
urred speech, tremor, vertigo,
rinary retention, blurred vision.
aradoxical reactions such as acute
yperexcited states, anxiety, halluci-
ations, increased muscle spasticity,
isomnia, rage, sleep disturbances,
imulation, have been reported;
ould these occur, discontinue drug.
olated reports of neutropenia,
iundice; periodic blood counts and
ver function tests advisable during
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Dermatology

Microflora of the Skin

NORMAL HUMAN SKIN contains both in and on its surface numerous bacteria. The bacterial flora of the skin is divided into two groups, resident and transient flora. The resident flora is relatively stable in both number and type of bacteria. Most of the resident bacteria are found on or at the surface of the skin; however, studies have revealed that bacteria may be found in the deeper layers of the epidermis. The source of the resident flora has been shown to be the sebaceous gland. Bacterial counts on normal human skin are higher in areas of high sebaceous gland activity. These counts will vary from individual to individual as well as from area to area and time to time in the same individual. Studies have shown a range of 1 to 1,000,000 per cm^2.

Resident Flora

The resident flora of the skin consists, for the most part, of the following bacteria: anaerobic or microaerophilic Corynebacterium acnes, Staphylococcus epidermidis albus, aerobic diphtheroids, E. coli, proteus and various mycobacterium. The mycobacteria are acid-fast and occur mainly in the external auditory canal and the genital and axillary areas. As a rule the anaerobes outnumber the aerobes 10 to 100 times. Most of these organisms may be classified as commensals (the mutual and inconsequential association between bacteria and higher organisms). It is interesting to note that bathing frequency does not materially affect plate counts.

Recent studies have led many investigators to the conclusion that these resident bacteria play an important part in protecting the individual from more pathogenic bacteria. For example, if Staphylococcus *albus* is present on the skin, it has been shown that it is difficult for Staphylococcus *aureus* to colonize in this location. When a patient is placed on one of the "mycin" antibiotics which are known to have high skin concentrations, Staphylococcus *albus* may be destroyed, and this is then followed with invasion by the more resistant Staphylococcus *aureus*. This is further demonstrated by the fact that neomycin-resistant Staphylococcus will reproduce and thrive under neomycin dressings, *but not until* the neomycin-sensitive organisms have been destroyed. This phenomenon is less common with systemic penicillin and its derivatives, for these drugs do not achieve high skin concentrations.

Transient Flora

Bacteria comprising the *transient flora* may be of two types. First there are those organisms that are normal saprophytes from soil, water and air. These may occasionally be cultured from the surface of the skin but are not permanent residents. An example of this type is Bacillus subtillis, a gram-positive, spore-bearing aerobic saprophyte. Such organisms are important only insofar as they may be confused with some related and pathogenic species, in this case Bacillus anthracis.

The second source of transient bacterial inhabitants is the normal flora of the nasopharynx and other body orifices. These organisms are transferred to the skin by the hands. In this group may be found such organisms as Staphylococcus *aureus,* Streptococcus pyogenes hemolyticus, H. influenzae, D. pneumoniae, N. meningitidis and Klebsiella pneumoniae. Recently increasing attention has been given to another group of organisms, that of the tribe Mimeae, especially Mima polymorpha and Herellea vaginicola. Mimeae are pleomorphic, gram-negative bacilli which resemble Neisseria and may normally be found as saprophytes in a certain percentage of the population. The skin, genitalia and mucous membranes are the principle reservoirs. It is now known that serious and at times fatal infections can be caused by this species.

It is a well recognized fact that for each of the above organisms a certain percentage of the population are healthy carriers and thereby provide a reservoir for new clinical cases. It can therefore be seen that the bacterial flora of the skin may vary from relatively nonpathogenic to highly pathogenic organisms, and that this bacterial population varies greatly not only in type but in number.

Willard C. Peterson, Jr., M.D.
Minneapolis, Minnesota

It's the Law

Hospital Liable for Urethral Tear From Catheter*

A man was injured in an automobile accident, suffering fractures of the pelvis and right tibia with bladder complications. One month following the injury while the patient was being moved by two orderlies, the catheter, which the orderlies did not know about, was accidentally pulled out. The following day a superpubic cystotomy with insertion of an indwelling catheter was performed. Two weeks later, a cystoscopic examination disclosed that the patient's ureter had been torn.

In the court case, the hospital was found liable for aggravating injuries, and specifically for the urethral tear.

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*Traina V. Ravenwood Hospital, Cir. Ct., Cook Co., Docket No. 64L-18447 (Ill., May 27, 1968). The Citation 17:12, October 1, 1968.

On Dropsies

All dropsies arising from acute diseases are bad; for they do not remove the fever, and are very painful and fatal. The most of them commence from the flanks and loins, but some from the liver; in those which derive their origin from the flanks and loins the feet swell, protracted diarrhoeas supervene, which neither remove the pains in the flanks and loins, nor soften the belly; but in dropsies which are connected with the liver there is a tickling cough, with scarcely any perceptible expectoration, and the feet swell; there are no evacuations from the bowels, unless such as are hard and forced; and there are swellings about the belly, sometimes on the one side and sometimes on the other, and these increase and diminish by turns.*

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*Hippocrates. The Book of Prognostics.

Case Reports

Cholecystocolonic Fistula

"CHOLECYSTOCOLONIC FISTULA" implies an abnormal communication between the gallbladder and the colon—two epithelial-lined surfaces. The report of a case and a review of the Mayo Clinic experience with cholecystocolonic fistulas from 1947 through 1966 follow.

Report of a Case

An 85-year-old white man entered this clinic in May 1967 complaining of anorexia and an "ill-feeling" of 1½ weeks' duration. Physical examination revealed an elderly gentleman in little apparent distress with an oral temperature of 103 F. There were a few moist rales at both lung bases and the roentgenogram of the chest revealed evidence of increased opacification of the lung bases bilaterally. Because of the bronchopneumonia he was hospitalized and treated with appropriate antibiotics after blood and sputum cultures had been obtained. He responded well. However, since the blood culture revealed *Escherichia coli,* an intensive search for the source of the septicemia was undertaken. A cholecystogram disclosed a small gallbladder containing stones and a fistula between the hepatic flexure of the colon and the gallbladder. The presence of the fistula was confirmed by barium enema (Figure 1).

The patient refused surgical treatment at this time, stating, "I'm too old for that sort of thing." He was dismissed with no special medication.

Between May and September 1967 the patient experienced occasional bouts of paroxysmal vomiting of brown material with accompanying midepigastric pain that radiated to the lower part of the abdomen bilaterally. The pain would last three to four hours and then disappear. He would sweat profusely with these attacks and thought his temperature was elevated. This syndrome had recurred every 10 to 12 days for two months prior to his rehospitalization, which was obviously required, in September 1967. His family had observed that he was jaundiced.

Physical Examination

The examination revealed a pleasant, healthy-appearing man with ruddy complexion. Blood pressure was 140 mm of mercury systolic and 90 mm diastolic, pulse rate 72 beats/min (regular), respiration 20/min, and temperature 98.4 F orally. The lungs were clear to auscultation and percussion. A grade 3 harsh systolic murmur, which extended to the right carotid artery, was heard at the aortic area. The liver edge was 1 cm below the right costal margin and the midepigastrium was slightly tender on palpation. The prostate was enlarged and indurated. The results of additional laboratory tests, including evaluation of hemoglobin, leukocyte count, differential count, urinalysis, prothrombin time, and serum protein, were all within normal limits. The serum bilirubin measured 1.4 mg/100 ml direct and 1.0 mg/100 ml indirect, the alkaline phosphatase 105 units, and the serum glutamic oxaloacetic transaminase (SGOT) 45 units.

Operative Findings

The patient submitted to laparotomy on September 11,

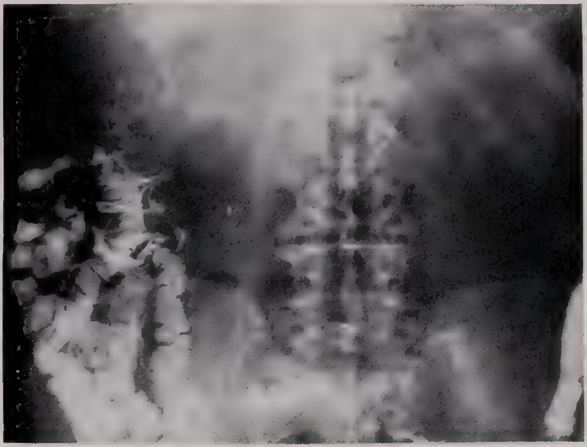

Fig. 1—Barium study of colon revealing filling of the gallbladder via a fistula.

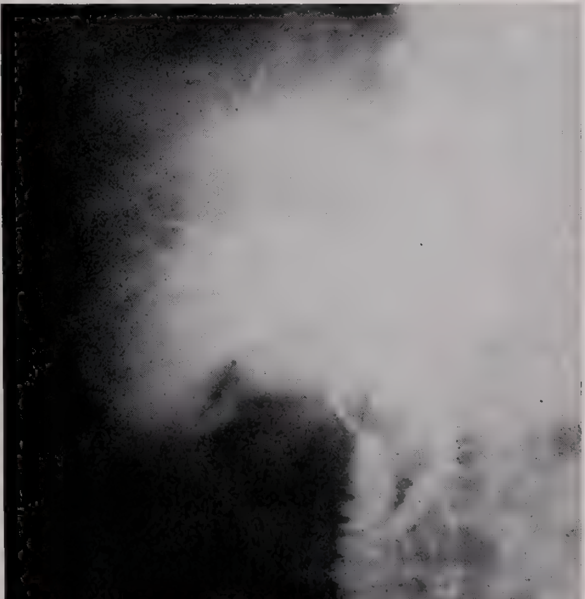

Fig. 2—Cholangiogram after operation, depicting a normal status.

1967, at which time a fibrous tract with a 5-mm lumen was found connecting the gallbladder and the hepatic flexure of the colon (after the omentum was dissected free from the area). The gallbladder contained stones, and both the cystic and the common ducts were dilated. The gallbladder with the tract was excised, the colon was closed, and the common duct was explored; sludge was removed but definite stones were not found. A cholangiogram showed the extrahepatic biliary ducts to be patent without residual obstruction. A T tube was inserted for prolonged drainage of the biliary tract. The patient did well after the operation. The only problem was nausea and vomiting, which lasted for 36 hours and then subsided spontaneously. The T tube was removed one month after operation and subsequent to repeated outpatient visits which continued to disclose an entirely normal state (Figure 2).

Comment

Incidence of the Lesion

Cholecystocolonic fistula is not a common complication of gallbladder disease. From 1947 through 1966, approximately 21,000 cholecystectomies were done at the Mayo Clinic and only 23 revealed cholecystocolonic fistulas. In 1925 Judd and Burden[1] reported a series of 153 cases of biliary-enteric fistulas, of which 26 (17%) were cholecystocolonic in type. (This incidence was slightly higher than that reported by Epperson and Walters[2] in 1953—seven of 84 (8%) biliary-enteric fistulas of cholecystocolonic type.)

This disease prevails among the elderly, the highest incidence being among persons in the eighth decade of life as the following data show: fourth decade, one; fifth decade, two; sixth decade, four; seventh decade, five; eighth decade, eight; and ninth decade, three.

Pathogenesis

The diagram of the sagittal section of the peritoneal cavity shows the proximity of the gallbladder and colon (Figure 3). Repeated attacks of cholecystitis and pericholecystitis in the presence of cholelithiasis could readily involve the hepatic flexure or the transverse colon in an inflammatory process, and necrosis with erosion of the walls of each of the viscera could result in formation of fistulas.[3,4] The element of surprise lies in the comparative rarity of this phenomenon.

Robson[4] has suggested that another mechanism of production could be formation of abscesses about the gallbladder with eventual erosion into the colon; the spontaneous drainage of such an abscess results in a fistulous tract.

It appears that cholelithiasis with or without overt cholecystitis is certainly a factor in the production of fistulas.[3] Twenty of the 23 patients in the series (1947 through 1966) had cholelithiasis, and nine had a definite history of repeated attacks of cholecystitis. In none of the cases in this series was malignancy or chronic ulcerative colitis an associated condition, although both have been reported as predisposing causes.[5,6]

Diagnosis

In spite of a thorough history, physical examination, and adequate laboratory aids, the condition can be notoriously difficult to recognize, as evidenced by the fact that in only 20% of the cases is the diagnosis made prior to operation.

Repeated attacks of fever and chills with mild to moderate jaundice and discomfort in the right upper quadrant were present in 50% of the patients.

Air in the biliary tree on x-ray examination of the abdomen is diagnostic, except for the rare case of reflux through the sphincter of Oddi. However, only two patients (9%) in this series had air in the biliary tree. Occasionally a radiopaque gallstone will be visible in the region of the sigmoid colon. A barium enema is useful, sometimes outlining the gallbladder and biliary tree as well as the fistula.

Cholecystography is usually not rewarding, since the majority of cases exhibit only a non-

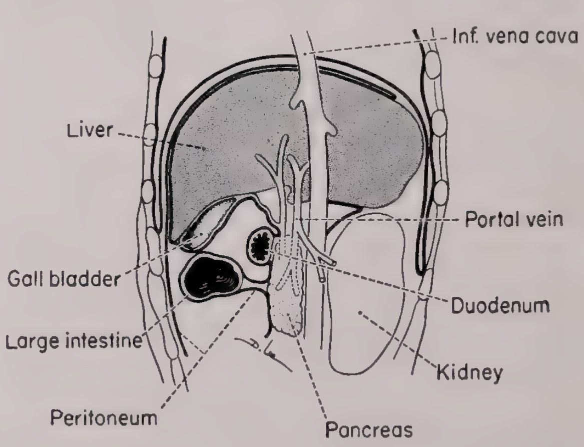

Fig. 3—Sagittal section of peritoneal cavity showing proximity of gallbladder to colon.

functioning gallbladder. Ten of the 23 patients were found to have a nonfunctioning gallbladder at cholecystography.

Complications

Ascending cholangitis with septicemia and jaundice is a frequent problem prior to surgical treatment. In this series 45% of the patients had a history of repeated attacks of fever, chills, and jaundice. Diarrhea and malabsorption can be troublesome and may result in loss of weight and vitamin deficiency.[7,8] A number of investigators have postulated that this may be caused by the presence of highly irritative bile salts in the colon. A hemorrhagic diathesis is sometimes present. In numerous cases fistulas presenting as massive gastrointestinal hemorrhage probably secondary to vitamin K deficiency have been reported.[9] Since the majority of the patients are elderly with other concomitant diseases, the surgical repair is not accomplished without a degree of morbidity and mortality. One patient in this series died one week after operation in congestive heart failure.

Treatment

Preventive

The most important single factor resulting in a decreasing incidence appears to be prompt removal of the diseased gallbladder.

Definitive

Cholecystectomy with closure of the fistulous opening into the colon, after adequate preoperative preparation of the patient, cures the disease. Present-day adjuncts, especially specific antibiotics, are extremely helpful.

Summary

Cholecystocolonic fistula is seen most commonly after repeated attacks of cholecystitis with cholelithiasis. It can be complicated by periodic attacks of ascending cholangitis, a hemorrhagic diathesis, and diarrhea and malabsorption with loss of weight. The preoperative diagnosis depends on a complete history, physical examination, and adequate laboratory aids, especially x-ray studies. The treatment is definitive: cholecystectomy with closure of the fistula after adequate preparation of the patient.

James H. Snider, M.D.*
Edward S. Judd, M.D.†
Rochester, Minnesota

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*Mayo Graduate School of Medicine (University of Minnesota), Rochester: Resident in Surgery.

†Mayo Clinic and Mayo Foundation: Section of Surgery.

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Traffic

There is never any traffic congestion on the straight and narrow path.
—Herbert Prochnow

Fine

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Warning: Activation of psychosis may occasionally be observed in schizophrenic patients. Do not use in patients under 12 years old, and do not use in women who are or may become pregnant unless the clinical situation warrants the potential risk.
Precautions: Careful supervision and protective measures for potentially suicidal patients are necessary. Discontinuation of therapy or adjunctive use of a sedative or tranquilizer may be necessary in the presence of increased anxiety or agitation, hypomania or manic excitement. However, phenothiazines may aggravate the condition. Atropine-like effects may be more pronounced (e.g. paralytic ileus) in susceptible patients and in those receiving anticholinergic drugs (including antiparkinsonism agents). Carefully observe patients with increased intraocular pressure. Prescribe cautiously in hyperthyroid patients and in those receiving thyroid medications. Cardiovascular complications (myocardial infarction and arrhythmias) are potential risks since they have occasionally occurred with imipramine, the parent compound. Desipramine may block the pharmacologic activity of guanethidine and related adrenergic neuron-blocking agents. Hypertensive episodes have been observed during surgery in patients on desipramine therapy. Before prescribing the drug, the physician should be thoroughly familiar with prescribing information, with the literature, with all adverse reactions, with the diagnosis and management of depression, and with the relative merits of all measures for treating the condition.
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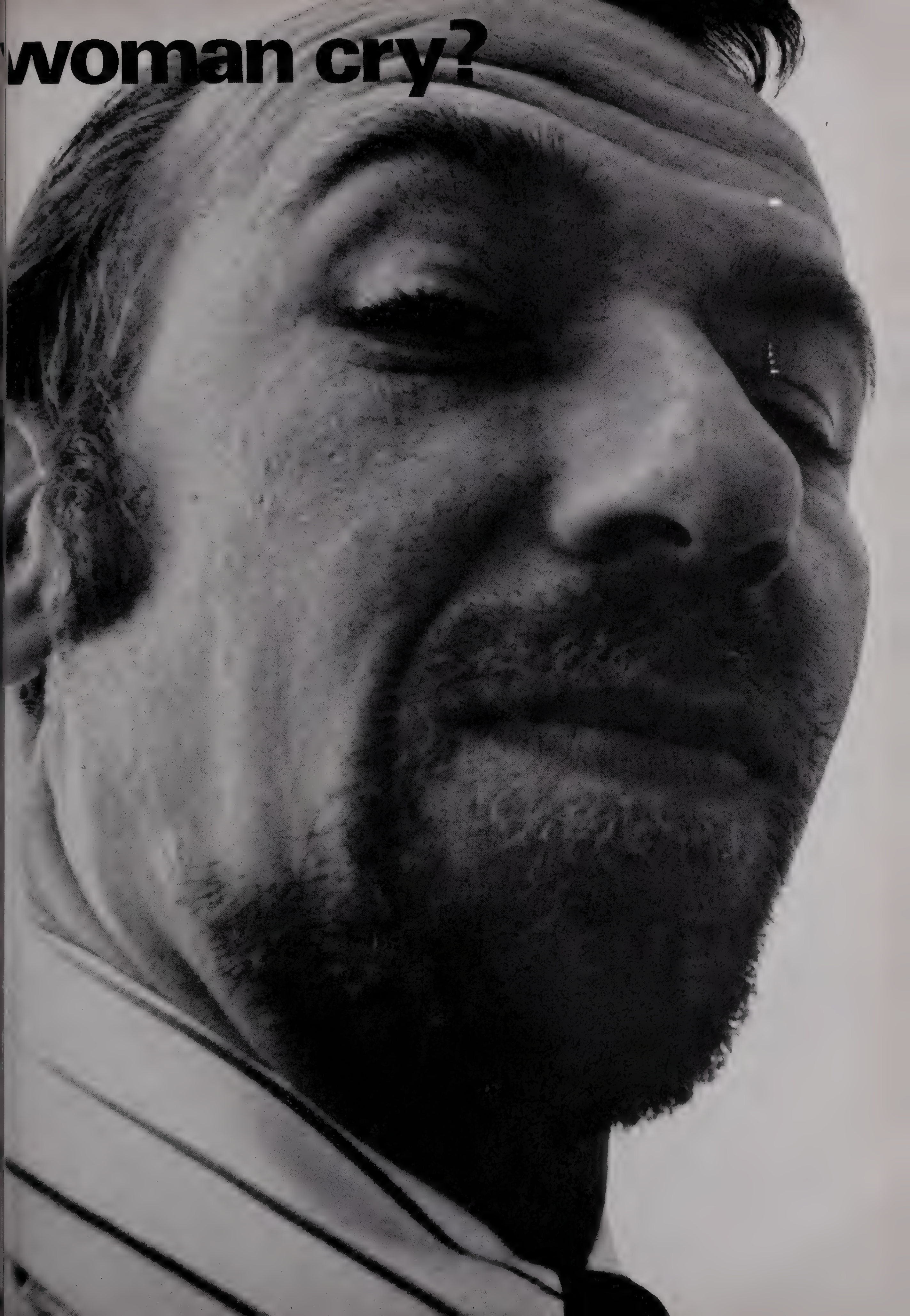

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Tybatran (tybamate) has been used with benefit in the treatment of depressive symptoms associated with anxiety and other symptoms of psychoneuroses. However, it is not indicated for primary treatment of depressive states. It is not an antipsychotic agent, although it has been used as adjunctive therapy in some psychotic patients.

Dosage: One 350 mg. capsule, 3 times daily and two at bedtime is suggested as the adult starting dose. Adjust to suit individual requirements. Daily doses above 3000 mg. are not recommended.

Contraindications: Known hypersensitivity to tybamate. Since no studies have been done with this drug in human pregnancy, it should not be used in pregnancy unless the potential benefit outweighs the risk.

Warnings: Administer cautiously to patients receiving phenothiazines or other CNS depressants or having history of convulsive seizures (See Adverse Reactions). Consider possibility of additive actions with alcohol or other psychotropic agents, particularly phenothiazines or MAO inhibitors.

Precautions: Avoid abrupt withdrawal after prolonged use, although withdrawal symptoms have not been reported to date. Exercise caution in addiction-prone individuals. If symptoms of hypersensitivity occur, discontinue at once and initiate appropriate symptomatic treatment. Avoid activities requiring optimal mental alertness if drowsiness or vertigo are present. As with any new drug, use cautiously in patients with history of drug allergies, blood dyscrasias, and hepatic or renal disease; periodic measurements of hepatic, hematopoietic and renal function should accompany prolonged and/or high doses.

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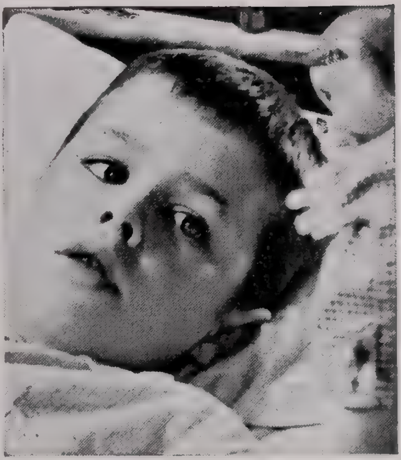

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Continued from page 1104

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Thought, not feelings, motivate the decisions of all truly great men.—Culinary Almanac

Book Reviews

Books are ships which pass through the vast seas of time.—Bacon

ATLAS OF PRECAUTIONARY MEASURES IN GENERAL SURGERY by Ivan B. Baronofsky; C. V. Mosby Co. 1968. $23.50.

Dr. Baronofsky has prepared an Atlas of "Defensive Surgery" in which he aims to point out surgical landmarks that may prevent certain serious complications if the operator can keep them carefully in mind during the procedure.

The introduction is written by Dr. Baronofsky's teacher, Professor Owen H. Wangensteen. The Professor obviously favors this approach for the surgeon confronted with the responsibility of familiarizing himself with certain details of an operation before undertaking it, and thus by "pre-visioning obviate the disasters of complications."

This Atlas contains 275 pages covering 25 procedures. The description is concise and the artistry of the illustrator, Daisy Stilwell, is superb. The various procedures described cover a rather broad area of general surgery, including some less common operations of particular interest to the author.

The author will no doubt receive a deluge of "why didn't you do — — — so-and-so, or why was this or that item not included?" However, a very broad area of experience has been employed. The section on gastric surgery is quite complete. The experience in this area has been particularly broad since, if this reviewer's memory serves correctly, the mere start of Dr. Baronofsky's experience began with 54 subtotal gastrectomies done during his chief residency.

Some doubts, however, might be raised by the author's praise of catheter duodenostomy, particularly since that particular method requires caution and perhaps in addition, an outline of the surgical tricks required to avoid the difficulties produced by the catheter itself. On page 74 a drawing of the mesocolon sutured to the jejunal loop is presented as an example of a *wrong* method; but it is identified as wrong only in the text. An unmistakable caption "WRONG" should be used, because a rapid reader might very well look at the drawings and by not carefully reading the text conclude that this is one of the methods to employ, whereas the illustration is used only as an example of error. The author's caution regarding the absolute necessity for operative cholangiography introducing dye into the duodenum before closing the abdomen might well be debated by those who feel that they can diagnose spasm by the character of the ending of the dye, even though it does not enter the duodenum.

This reviewer suggests that this Atlas of General Surgical Procedures is a very useful book for the resident and at times might be helpful to the surgeon who wishes to review an unfamiliar area.

J. H. Strickler, M.D.
Minneapolis, Minnesota

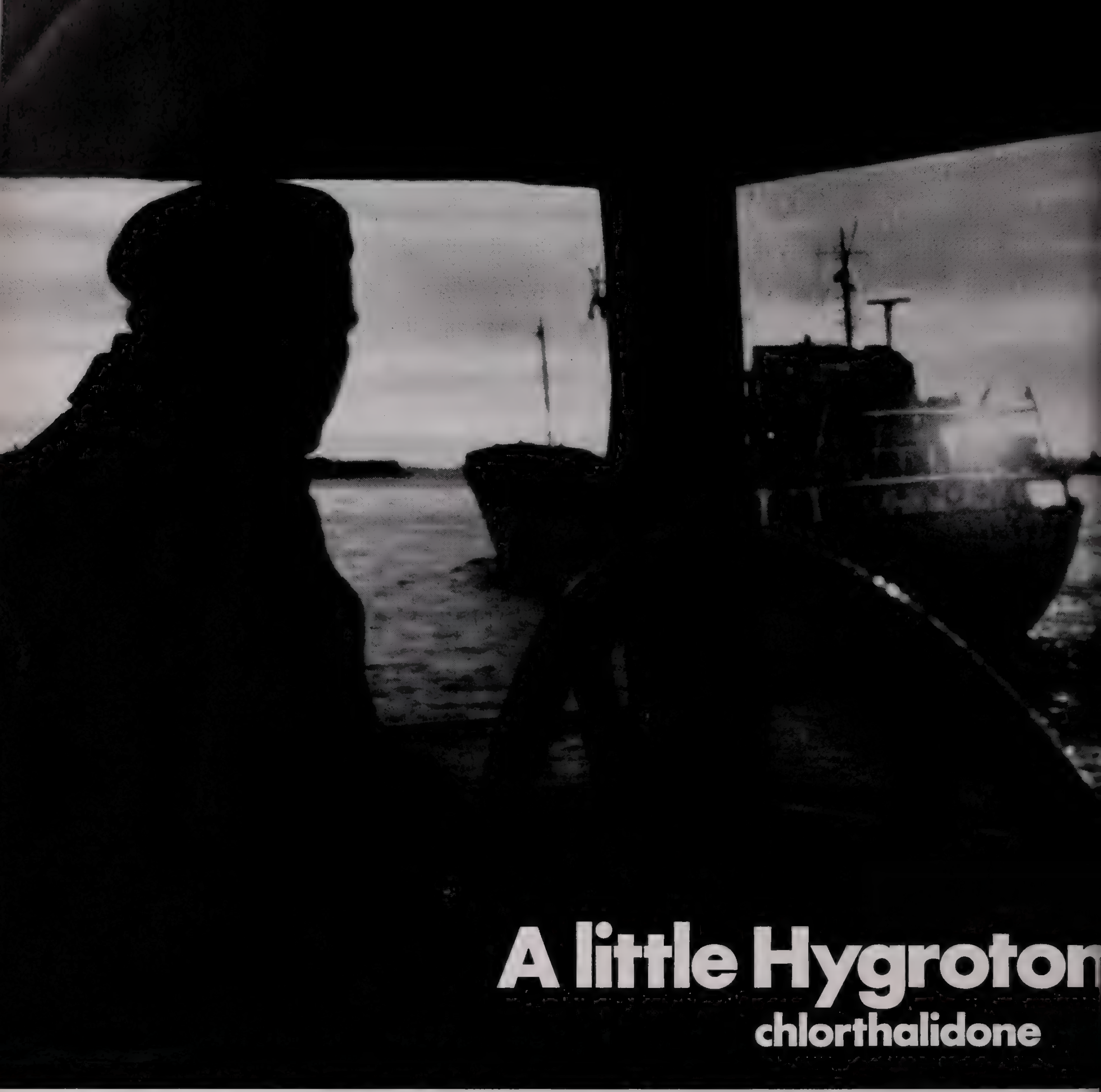
COMPREHENSIVE REVIEW FOR MEDICAL TECHNOLOGISTS, edited by Francis E. Dolan, Ph.D., Professor of Anatomy and Physiology, and Chairman, Department of Medical Technology and Biology, University of Bridgeport, Connecticut. C. V. Mosby Company 1968, pp. 155. $6.95.

The purpose of this multiauthored booklet is to aid the preclinical trainee in medical technology preparing for the National Registry Examination and the medical technologist who has been away from the field for many years. These two objectives are accomplished by compiling 603 questions and answers covering ten disciplines in medical technology: clinical chemistry, pretransfusion and blood bank, serology and immunology, bacteriology, hematology, parasitology, mycology, histology including cytology, urinalysis and clinical microscopy, and miscellaneous techniques. The latter includes 35 items, among them microscope, stains, reagents, anticoagulants, sterilization, etymology, mathematics. Though anatomy and physiology are not listed as disciplines, Dr. Dolan has devoted 30 pages and 157 questions and answers to these subjects. According to medical technologists I have consulted, these fields are not part of the National Registry Examination.

In Chapter 9, "Hematology," the question "What are Cabot's ring bodies?" is answered "—are seen in anemias, possibly representing nucleic acid not incorporated into hemoglobin." This leaves the student with the impression that Cabot rings occur in all anemias. This is not the case. If there is tangible histochemical evidence that nucleic acids, hemoglobin and Cabot rings are related, it is not common knowledge, and the original source for this answer should have been cited. Many other debatable answers and lack of literature references do not encourage me to recommend this booklet as an authoritative work to medical technologists, but I am inclined to approve it as an aid to the preclinical trainee preparing for the National Registry Examination.

The C. V. Mosby and Company has done a fine job selecting the printing type, presenting the text in a two column form, and binding the booklet.

Emil Maro Schleicher, Ph.D.
Minneapolis, Minnesota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HY-6674

Special Article

Trichinosis Outbreak in Minnesota and Iowa*

Associated with Consumption of Summer Sausage

LESLIE P. WILLIAMS, JR., D.V.M.†
Fort Collins, Colorado

C. B. NELSON, M.D.‡
Minneapolis, Minnesota

CARL L. ZYMET, D.V.M.#
Ossining, New York

In the five-year period 1960 through 1964, an average of 233 (range 306-160) trichinosis cases per year have been reported in the United States, with an average mortality of 3.4 deaths per year. During the same time period, six cases were reported in Minnesota and 33 in Iowa.[1,2,3,4,5] These usually occurred as sporadic cases, and the source of the infection was difficult to ascertain; however, when several cases were related in time and place, as indicated by a laboratory receiving a number of sera with requests for a trichinosis test, or through epidemiological follow-up at the suggestion of a practicing physician, the source was often determined.[6,7,8,9] Roselle et al. tested a sample of bear meat, and trichinella larvae were demonstrated. In the other reports, no portions of the suspect meat could be found, and epidemiological evidence was relied upon to demonstrate that commercially ground hamburger[7,8] and ground ham[9] were the most probable vehicles of infection.

This is a report of an epidemic involving 44 Minnesota and Iowa residents (37 cases and seven suspected cases) living in the vicinity of a combination butcher-shop lockerplant near the border of these two states. The most probable source of this outbreak was smoked summer sausage that was produced by this plant and consumed around Thanksgiving, 1964. In addition to being a large outbreak, one death was associated with it. The persons involved were designated as cases, or suspect cases, on the basis of clinical histories, eosinophil counts, and the results of one of two serologic tests for trichinosis. In Minnesota the Bentonite flocculation test (BFT)[10] is used*; Iowa uses the Sussenguth-Kline.[11]

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*From the Minnesota Department of Health, Minneapolis, Minnesota, and the National Communicable Disease Center, Public Health Service, U.S. Department of Health, Education and Welfare.

†At the time of this investigation, Dr. Williams was Epidemic Intelligence Service Officer (NCDC) assigned to the Minnesota Department of Health. He is presently an Associate Professor, Department of Microbiology, College of Veterinary Medicine, Colorado State University, Ft. Collins, Colorado.

‡Chief, Section of Acute Communicable Disease, Division of Disease Prevention and Control, Minnesota Department of Health.

#At the time of these investigations, Dr. Zymet was Epidemic Intelligence Service Officer (NCDC) assigned to the Iowa State Department of Health. He is presently in the private practice of Veterinary Medicine, Ossining, New York.

The Epidemic

On January 4, 1965, a physician called the Minnesota Department of Health to report a possible trichinosis outbreak beginning on December 13, 1964. Approximately 15 persons experienced symptoms compatible with this disease and had eosinophil percentages ranging from 12% to 54%. Three patients required hospitalization, and one of these died on January 1. The physician at first suspected a contagious viral illness and, in order to confirm this diagnosis, requested a white blood count and differential counts on seven of the eight nurses, the laboratory technician in the local hospital, and herself ten days after the three cases had been hospitalized, since these individuals might have been exposed. All had counts within normal limits. None of them experienced any illness. These findings reinforced the doctor's second diagnosis, trichinosis.

The Initial Cases

A preliminary investigation revealed twenty-four possible cases ranging in age from four to 65 years. The most common symptoms were myalgia, intermittent fever, malaise, periorbital or facial edema, vomiting, diarrhea, conjunctivitis, and abdominal cramps. One of these suspect cases was a butcher in Minnesota who operated a combination locker-plant and butcher-shop in a very small town near

TABLE I

Identifying Data and Laboratory Results from Trichinosis Cases Showing Comparison of BFT and S-K Results, Minnesota-Iowa Outbreak, 1964

Case Number	Age	Sex	Onset of Illness	Percent Eosinophils	BFT TEST #		S-K TEST #
					1/14/65	3/2/65	3/2/65
4A*	10	M	12/16/64	10	NT†	1:160	1:32
B	33	F	12/14/64	16,5	1:10	1:80	1:32
5A	33	F	12/21/64	54,18	Neg.	1:10	1:16
7A	30	F	12/15/64	40,8	1:80	1:40	1:16
B	31	M	12/13/64	44,24,15	1:40	1:80	1:32
C	6	F	12/15/64	8,17	1:40	1:20	1:32
8A	49	M	12/20/64	18,9	1:5	Neg.	1:4
9A	50	M	12/15/64	7	NT	1:60	1:32
10A	32	F	1/2/65	8	NT	1:160	1:64
11A	36	F	12/24/64	4	NT	‡	1:4
B	36	M	1/8/65	13	NT	1:10	1:8
C	14	F	12/15/64	3	NT	1:320	1:64
12A	42	M	12/23/64	24,15	1:40	1:40	1:32
B	11	F	12/18/64	29,27,16	1:20	†	1:64
C	9	F	12/22/64	51,27,17	1:80	1:160	1:32
D	9	F	1/4/65	6,17	1:20	1:5	1:8
E	6	M	12/18/64	8	NT	1:10	1:8
13A	39	M	12/28/64	12	NT	1:20	1:16
B	46	F	12/29/64	18	NT	Neg.	1:16
C	14	M	12/16/64	13	NT	1:20	1:16
D	12	M	12/22/64	16	NT	1:5	1:8
E	11	M	12/24/64	10	NT	1:5	1:8
14A	52	M	12/2/64	15,18,12	1:20	Neg.	1:4
B	43	F	12/20/64	19,16	1:20	1:160	1:64
C	21	M	12/22/64	12,12	1:10	1:80	NT
D	20	F	12/21/64	15,19	1:40	1:320	1:64
15A	33	M	12/14/64	16,1	1:160	1:320	1:256
16A	50	M	12/24/64	15	NT	1:20	1:16
B	47	F	12/10/64	6	NT	1:160	1:64
17A	50	M	12/24/64	NT	NT	1:10	NT
18A	65	M	12/17/64	53,27	1:40	NT	NT

*Arranged in family groups where possible.

†Tube broken in shipment.

‡Not tested. These cases were not brought to our attention until our second visit to the area, or for other reasons no test was done.

#BFT considered positive at 1:10 and S-K at 1:4 titer.

---

*This test is performed at the National Communicable Disease Center.

the Minnesota, Iowa, Wisconsin borders. About a week later two of us (LPW and CBN) visited the area, collected blood specimens for the Bentonite flocculation test[10] and eosinophil counts, and obtained further clinical data. When the Bentonite flocculation test results were received from the National Communicable Disease Center, Atlanta, Georgia, the two neighboring states were notified of the outbreak. No cases in Wisconsin were connected to this outbreak. A check of the records of the State Hygienic Laboratory of the Iowa State Department of Health uncovered one case in Northern Iowa, where the attending physician had requested a Sussenguth-Kline[11] test for trichinosis on January 6. The result was a 1:64 titer. Subsequent investigations brought six more cases to the attention of Iowa authorities.

Two months later, we again contacted the cases and collected blood specimens from them. The names of an additional twenty possible cases were obtained and most of these persons were interviewed and a blood specimen was collected. Fourteen were determined to be cases on the basis of clinical history and laboratory findings. The list of cases that were initially diagnosed by Bentonite flocculation test or by the Bentonite flocculation and Sussenguth-Kline tests are shown in Table 1. A Bentonite flocculation test titer of 1:10 or higher is considered indicative of current infection. A Sussenguth-Kline titer of 1:4 or higher is considered positive by Iowa health officials. Where three eosinophil percentages are shown, the first one listed was derived from the differential counts requested by the private physician prior to our investigation of the outbreak. Those cases intially diagnosed by the Iowa State Hygienic Laboratory, using the Sussenguth-Kline test, are shown in Table 2. The data of an additional seven persons having symptoms compatible with the disease but no supporting laboratory findings are shown in Table 3. The dates of onset of clinical symptoms are shown in Figure.

The Common Vehicle

The only common meat food items consumed by the majority of the persons between the last week of November and the second week of December was summer sausage from Case 8A's locker plant. Twenty-seven persons had either purchased or consumed summer sausage during this period, or had definite knowledge that they had eaten it at a party; thirteen stated that they thought they had eaten it at a party or that they

TABLE 2

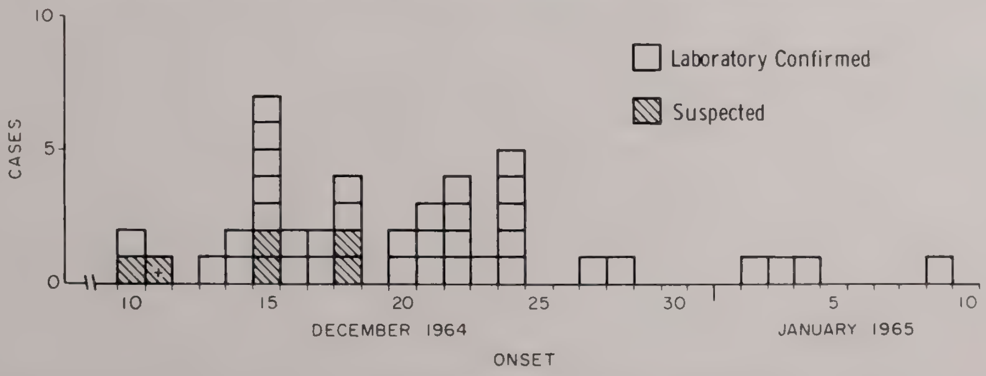
Identifying Data and Laboratory Findings of Trichinosis Cases Initially Diagnosed by the State Hygienic Laboratory, Iowa State Department of Health Minnesota-Iowa Outbreak 1964

Case Number	Age	Sex	Onset of Illness	Percent Eosinophils	S-K Test† Date	S-K Test† Result
0A	24	M	12/22/64	26	1/6/65	1:64
1A	?	F	?	NT	3/1/65	1:4
2A	26	M	1/3/64	11	2/4/65	1:4
3A	23	M	12/24/64	NT	2/2/65	1:256
4A	10	M	12/16/64	10	2/1/65	1:64
C*	62	F	12/15/64	NT	2/1/65	1:64
6A	18	F	12/17/64	NT	2/1/64	1:8

*Grandmother of 4A; resident of Illinois.

†S-K test considered positive at titer of 1:4.

TRICHINOSIS CASES* BY DATE OF ONSET, MINNESOTA - IOWA OUTBREAK, 1964-1965



*Total 44; one date unknown; one suspected case had no definitive symptoms.
+Patient died Jan. 1, 1965.

Figure

ate it frequently and thought they had bought some in early December. The experience in two of the cases was of special interest. The resident of Illinois, 4C, was in the outbreak area only from November 16 to November 23, 1964. She ate summer sausage near the end of her visit. Seventeen A was clearing timber for 16A on December 5, 1964. During the work day, 16A shared his lunch of summer sausage sandwiches with him. This was the only time 17A ate this meat during November and December to the best of his wife's knowledge. Sixteen A stated that he bought summer sausage only from 8A's locker.

The patient, 19B, who died, was a 52-year-old farmer. He was seen by his physician on December 18, with a history of illness of one week, characterized by upper abdominal pain, vomiting, backache, malaise, and generalized muscle pain. His eosinophil percentages while he was in the local hospital, were 28, 25, and 17%. He was then transferred to a Wisconsin hospital where his differential counts were 13 and 17% eosinophils and his absolute blood eosinophil count was elevated to 821/cu. mm. He experienced severe diaphragmatic pain and spiking fever. Trichinella skin and latex tests were negative. Agglutination tests for brucellosis, typhoid, paratyphoid and proteus were negative. The L.E. cell test was negative. No ova or parasites were found in his feces. Skin tests for histoplasmosis, coccidiomycosis, and North American blastomycosis were all negative. His blood culture was sterile. He died unexpectedly on January 1. Trypsin digestion was done on several muscle specimens but no larvae were recovered. The pathologist's report states: "Although these sections present a characteristic pattern of lesions compatible with trichiniasis in the skeletal and cardiac musculature, we have been unable in several hundred sections examined to identify the larvae and encysted form of the parasite. . . . We have labelled this case one of presumed trichiniasis" (personal communication, Dietz,[12] 1965).

Preparation of the Sausage

Eight A stated that pork butts used in the manufacture of summer sausage were purchased only from United States Department of Agriculture-inspected meat plants. The butts were boned, boxed, and held at −5°F for 30 days as recommended by the Minnesota State Department of Agriculture to kill trichina larvae. The meat was then thawed, ground and mixed with United States Department of Agriculture-inspected beef, put in natural beef casing and smoked for three days at 110°F. His total sales were about 600 pounds a month (wholesale and retail). Six B bought summer sausage wholesale and sold it to several small Iowa food markets in the area (an illegal act in interstate commerce since it was not produced under United States Department of Agriculture supervision). Since 8A seemed very conscientious about complying with the state recommendations, we can only speculate as to the possible source of the outbreak. It seems most likely that either a grinder was left uncleaned after being used for sausage making or that an unfrozen pork butt was used in the making of summer sausage by mistake. In all

TABLE 3

Identifying Data and Laboratory Results of Persons Suspected of Having Trichinosis Associated with the Minnesota-Iowa Outbreak, 1964

Case Number	Age	Sex	Date of Onset	Resident of	Percent Eosinophils	Laboratory Test		
						Date	Test	Result
19A	57*	F		Iowa	24,22	11/14/65	BFT	1:5
						3/2/65	BFT	Neg.
						3/2/65	S-K	1:4
B	52†	M	12/11/64	Iowa	28,25,17,18	—	NT	NT
12F	34‡	F	12/18/64	Minn.	7,4	1/14/65	BFT	Neg.
						3/2/65	BFT	Neg.
G	8	M	12/18/64	Minn.	9	—	NT	NT
7D	8	M	12/15/64	Minn.	NT	—	NT	NT
6B	50	M	12/15/64	Iowa	12	—	NT	NT
C	42	F	12/10/64	Iowa	NT	—	NT	NT

*Suspect case experienced no definitive symptoms.

†Suspect case died January 1, 1965.

‡12F had leukemia. Had cobalt irradiation treatment within six months of first test.

probability, only one lot of 200 pounds was infested with larvae. However, none of the suspect sausage could be recovered for examination.

Discussion

A previous series[13] reviewed the occurrence of trichinosis in the State of Minnesota from 1913 to 1947 and reported on 37 clinical cases in a small village. The similarities between the 1947 outbreak and the present one included similar symptom complexes, some very high eosinophil counts, patients of predominantly Central European stock, and a history of having consumed smoked summer (country) sausage. It was also noted in this report that pork had been involved in all cases in Minnesota where a source of trichinosis had been suspected or found.[13]

The usual incubation period is five days but may be as short as 18 hours or as long as 28 days.[13] During this stage gastroenteritis may occur;[13,14] one half of our patients experienced one or more symptoms of gastroenteritis. The next stage is that of muscle invasion and larval migration when the symptoms usually associated with this disease occur.[14] Eosinophilia occurs in the second week, usually peaks in the third week, and gradually decreases over several months. Myocarditis is the most serious complication of trichinosis and is the usual cause of death. Approximately 26% of the patients with myocarditis will show electrocardiographic changes, but clinical evidence of these changes is usually absent. Larvae invade the myocardium but do not encyst there.[15,16] No electrocardiographic changes were reported from 19B's tracing made eleven days after the onset of his symptoms.[17]

Twenty-seven serum specimens collected on March 2, 1965, had both the Bentonite flocculation test and the Sussenguth-Kline test completed. Seven of these (26%) were not positive by the Bentonite flocculation test (titers less than 1:10) but were positive by the Sussenguth-Kline test (titers greater than 1:4). These data support the findings of Norman and Kagan (1963) from several comparison studies of these and other diagnostic tests for trichinosis. Maynard and Kagan stated that the Bentonite flocculation test has the most value in acute stages of infection and that the Sussenguth-Kline test is of particular worth in detecting chronic infections. They believe that the Bentonite flocculation test is a most valuable test due to excellent specificity and sensitivity that will detect individuals with antibody from a current infection.[14] There is agreement between these statements and the recent research by National Communicable Disease Center workers in evaluating trichinosis tests to detect swine infections. The Sussenguth-Kline test was one of their tests of choice because it becomes positive early in experimental disease and continues positive for a long time.

The preventive measures against trichinosis set forth by the American Public Health Association are briefly:[20]

1. Adequate processing of pork products and separate grinders for pork where processing requires grinding of meats from various animals.
2. Cooking of garbage and offal fed to swine.
3. Education of the public to cook all fresh pork or pork products for a time and at a temperature such that all parts of the meat reach at least 65.5°C (150°F) if not processed under United States Department of Agriculture regulation.
4. Freezing of pork or pork products to −27°C (−16°F) (central portion temperature) for 36 hours.

The U.S. Department of Agriculture regulations state that meat products, not customarily well cooked in the home, shall be heated to an internal temperature of 137°F or higher, or frozen at 5°F for 20 days, −10°F for 10 days, or −20°F for 6 days.[21] Eight A's treatment of the pork used in his summer sausage was adequate and complied with State recommendation; however, his treatment was not terminal or applied to the completed product. The United States Department of Agriculture requirements offer a greater protection for the consumer by treating the finished product, thus insuring against such an error as was probably responsible for this outbreak.

Summary

A trichinosis outbreak involving Minnesota and Iowa residents was investigated during the first quarter of 1965. Thirty-seven cases were identified. Diagnosis was based on clinical symptoms, food histories, eosinophil percentages, and the results of the Bentonite flocculation test and/or the Sussenguth-Kline test. One person associated with the outbreak died of presumed trichinosis. The epidemiologic evidence supported the hypothesis that the vehicle of infection was one lot of summer sausage prepared at and sold from a small combination-locker plant-butcher shop located in Minnesota near the Iowa border.

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No Time for Laughing

An eighty-year-old man kept a detailed record of what he had done during each hour of every day and then figured out how he used his time during the entire period of his long life. He spent over twenty-six years in sleep, twenty-one years working, two hundred and twenty-eight days shaving, and one hundred and forty days paying bills. He also spent over twenty-six days scolding his children and two days yelling at his dogs. Only twenty-six hours were spent in laughing.*

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*Walter Dudley Cavert, Remember Now.

The Beautiful People

As a nation we've been going soft; well on our way to becoming a country of beauty-rested sissies. How many of us can run around the block without puffing? How many of us can work a full, hard day without using up our last ounce of energy? We've long prided ourselves on our comfortable life. Perhaps it has been too comfortable.*

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*Dr. Victor Heiser; R.N., A Journal for Nurses.

The James E. Moore Society

Man's Early Challenge to Neoplasms*

DURING THE PAST SEVERAL decades man has greatly increased his scientific knowledge and understanding of the origins and nature of life and of disease affecting life.

A Neoplasm

The nature and etiology of cancerous processes has defied man to a much greater extent than those of many other illnesses. Cancer is a disease that acts in a very special way: flesh acting insidiously upon itself in a proliferative, uncontrollable and predatory manner. Each lesion is a cancerous process made up of cells derived in most instances from the host organism, which has been so altered that it no longer obeys the laws of a multi-systemed unit where each cell must peacefully co-exist with the other cells. Instead, chaos may occur, with the altered cells so multiplying at the expense of normal cells as to result in the mortality of the host. This process is called neoplastic; the part that is changed by the process is a neoplasm.

Era of Empiricism (to 1761 A.D.)

Early in man's history, mysticism so pervaded all departments of life that many of its ideas still prevail in our medicine and folklore. Considering the length of time that man has dealt with this disease, we must admit that his knowledge of its nature and treatment have not progressed very fast or far. Some of the original descriptions of cancer are still valid even today.

Origin of the Word

The use of the term "carcinoma-cancer" was initiated during Greek times, probably because of the observation that malignant growths had multiple large veins around them. Galen said that these growths were called cancer because: "As a crab is furnished with claws on both sides of the body, so in this disease the veins which extend from the tumor represent with it a figure much like that of a crab;"[22] and in 625 A.D. Paul of Aegina said: "However, some may say that cancer is called such because it adheres with such obstinacy to the part it seizes that like the crab, it cannot be separated without great difficulty."[22]

Occurrence in Ancient Times

Written records of archaeological findings in Egypt and Peru reveal the existence of osteoporosis, osteosarcoma, and osteomalacia. The earliest medical records,[6,7] dating back to about 2500 B.C., were found in China, in India and in the Egyptian papyri. In the Papyrus Ebers (1500 B.C.) a tumor is mentioned, and it is said, that "such a tumor must not be touched," suggesting that the result might be fatal. The only clear description of cancer is that of a lipoma, which was treated "with a knife." In a cuneiform inscription from Nineveh (800 B.C.) cancer of the breast is mentioned. Hebrew writings[5] contain clinical descriptions of symptoms diagnostic of malignant growths.

Early Treatment of Neoplasms

In Greek history Democedes is credited with successfully treating his wife for cancer of the breast. Therapy during that time was based on excision and a variety of escharotics and arsenical ointments. Hippocrates differentiated between scirrhus and carcinoma, the former being a hard and the latter an ulcerating type of cancer. The Hippocratic Canon, the first to employ the terms cancer and carcinoma, contained references to cancer of the breast, stomach, and uterus, and extirpation of a neck cancer by cautery.

Celsus (35-25 B.C.) believed the disease to be generally incurable, but he operated on local ones. He made many diagnoses of cancer by its recurrence after cautery and caused one of his contemporaries to remark: "Cancer is incurable because it cannot be curable; if curable then it is not cancer." Leonides of Alexandria (180 A.D.) was the first to describe retraction of the nipple in breast cancer. He operated on many cases of breast cancer by excision of the breast with a scalpel, making sure in all instances that he was going through sound tissue, and cauterizing the wound to prevent hemorrhage and to destroy the remaining cancer around the incision.

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*Presented to the James E. Moore Society on October 8, 1968.

Galen (131-203 A.D.), the great Greek physician during Roman times, described a certain diet to be followed by the cancer patient. Also, by prescribing purgative remedies and bleeding, he sought to influence the course of the tumors.

During the 12th and the 14th centuries, the surgical works of Rolando and of Guy de Chauliac carried on the conservative Galenic attitude toward cancer. Localized and superficial tumors were treated with caustic pastes or excised with the knife and/or cautery. Cancers of any great proportions, however, were left alone. Only one late Renaissance German surgeon, Fabricius Hildanus, carried out comparatively drastic operative resections for cancer, performing in some instances a crude axillary dissection.

Etiology of Cancer

Galen's humoral theory dominated medicine for more than fifteen hundred years. According to this theory, the body was regarded as having four fluids: blood from the heart, phlegm from the head, yellow bile from the liver, and black bile from the spleen. Any abnormal mixture of these resulted in disease. Galen thought that cancer developed from concentration of the black bile, suggesting that the suppression of the menses and the appearance of hemorrhage prevented the discharge of black bile.

Period of Gross Pathology (1761-1838)

Prior to 1761, cancer was often confused with inflammatory processes. During the Renaissance great advances in anatomy and wound surgery were achieved; but pathology did not succeed in escaping from the bounds of the humoral theory. Until the dogma of this theory was discarded and the classification of tumors begun, on the basis of objective findings at autopsy, improvement in diagnosis and treatment was impossible. In the 17th and the 18th centuries new explanations were sought, consistent with newly evolving pathological concepts.

The Nature of Cancer

In 1761, Morgagni,[23] an anatomist, laid the foundations of pathologic anatomy on the organ level, after finding localized cancer in many of his autopsies. He distinguished malignant neoplasms from benign swellings such as aneurysms, strumas, gummas and erosions. A French surgeon, LeDran, at this same time, was the first to totally discard Galen's humoral conception of cancer. He also regarded cancer as a local disease in its early stages and believed it spread systemically via the lymphatics to regional nodes and then into the general circulation. He described fully the path of metastasis to the lung from breast cancer.

Research into the cancer problem was being stimulated by scientific societies. The French Royal Academy of Surgery in 1732 and the Lyon Academy of Science in 1773 offered prizes for original essays on the question: "What is Cancer?" The latter award was won by the surgeon-chemist Bernard Peyrille. He inoculated a dog with fluid from human mammary cancer; but the dog was described as barking so much that Peyrille's housekeeper drowned the animal.

Modern Etiology

In 1775, Percival Potts,[25] studying scrotal cancer in chimney-sweeps, strengthened the concept of chemical and *physical irritants* as aggravants for neoplasma. John Hunter, in his "Lectures on the Principles of Surgery," said: "I would call that cancer which produces the following effects: viz, a circumscribed tumefaction with much hardness and a drawing in of the skin covering it, as if the cellular membrane underneath it was destroyed; then a species of suppuration takes in the center and ulceration of the external surface. . . Cancer is one of the first class of our first division of poisons; viz, that which only produces local effects through it has been supposed to contaminate the constitution, which would be terrible indeed, as we have no specific nor even palliative treatment for it." Upon the cause, he wrote:

> "It has been said that cancers are produced by *ill health* as rheumatisms are; but this arises from the age of cancer being the age of such complaints and being the predisposing cause of both, but not particularly, of the cancerous disposition. The pre-disposing causes are three in number, viz, age, parts involved and *hereditary pre-disposition,* and perhaps *climate* also has a considerable effect though not itself a pre-disposing cause."[9]

He suggested that tumors, although products of lymph secretion, were structurally comparable to normal organs.

The first cooperative group to enter into the study of cancer, following the impetus given by John Hunter, comprised a number of prominent English clinicians who in 1802 organized themselves into "The Society for Investigating the Nature and Cure of Cancer."[1] This society aroused contemporary interest in cancer by sending to medical practitioners a questionnaire which covered many clinical aspects and speculative inquiries designed to obtain a consensus of opinion with regard to heredity, infections, climate, and a host of other factors which might influence the development of cancer. These questions were posed in order to improve clinical observations and diagnostic techniques. A reply to these queries was published by a Dublin surgeon in 1809 who de-emphasized suspected hereditary and infective influences and stressed the constitutional source of cancer as a deficiency of ferrous oxide.

Cellular System

In the French School of Medicine the practice of pathologic anatomy begun by Morgagni was continued by Bichat,[26] who distinguished stroma and parenchyma in rudimentary terms, the former of which he designated a "cellular system" common to all tumors. Laennec[27] implemented these ideas (1812) when he classed cancers among the heterologous, adventitious tissues; tissues which do not have normal organ counterparts but are *de novo* productions of pathologic processes. He attempted to improve the descriptions of neoplasms by observation of microscopically thin sections, but his work in this area was largely disappointing because of limitations in lenses for microscopes. His theories were based on his belief that neoplastic growth was basically a degenerative process. Dupuytren tried to establish the infectiousness of cancer by feeding and inoculating animals with fragments of malignant tissue from humans. Cruveihier believed that the only difference between these forms as described by Laennec stemmed from the relative amounts of "cancer juice" occurring in each. Colloid cancer was distinguished from other types as containing no "cancer juice."

An opposite view was taken by Broussais who felt that neoplasms were manifestations of change in the constitutional "tone" or vigor through alterations in the organism's inherent irritability. He proposed that except for superficially localized instances, cancer, as a generalized consequence of inflammation, was incurable. His research sought its causes in the various pathways of irritation culminating in inflammation. Further modification of this idea was advanced by a colleague (Andral),[3] who defined cancer not as a specific structural lesion but as a product of nutritive alterations and aberrant secretory activities to which inflammation was a contributing cause.

Period of Microscopic Pathology (1839-1900)

Blastema Theory

The application of the achromatic microscope (Müller) to the tumor problem in 1838 constituted one of the major advances in the 19th century to cancer research and diagnosis. Müller noted the predominance of connective tissue in scirrhus, differentiated the stroma of adenoid tumors from their parenchyma and also detected within these cellular groups such things as nuclei, granules, fat bodies, and other inclusions. With this evidence, he tried to correlate clinical symptoms with microscopic appearances. His assumption was that tumors grew from separate germinal elements within the parenchyma. This theory was called the Blastema Theory from which, with modifications, the specific-cell concept evolved.[3] Proponents of this theory suggested the existence of a unique germinal layer, the "cancer blastema," through which all new autonomous growths evolved. Using this principle as the cornerstone of his Cellular Pathology,[30] Virchow considered it possible that cancer originated not from free "blastema" (intercellular plastic lymph), but from the blastema within pre-existing cells. In addition, he assumed that connective tissue played an essential role in the formation of tumors. This theory suggests that the neoplasm begins in the cellular elements of this tissue and then invades the involved tissue.

Epithelial Theory

An early counter-current to Virchow's Connective Tissue Theory was advanced by Carl Thiersch and reinforced by Waldeyer. The former established that epidermal tumors were firmly bound with the connective tissue and that reproduction of the parenchymal element was followed by stromal growth. Thiersch followed these growths in neoplastic alterations with the following conclusions:[3] (a) the stroma, although it sustains epithelial growth in a variety of ways, is not the germinal basis of this growth in health or disease; (b) epithelium possesses its own germinal identity and is the source of distinct formations in health and disease; and (c) it is necessary to alter the thesis that "a tumor is analogous to any other new formation and results from the proliferation of cells of the same general character as the tumor." This is called the Epithelial Theory; it specified that all cancer cells were atypical versions of normal epithelial cells, not of the particular cell, but rather the behavior of the whole group of cells as distinguished by increased mitotic figures, aberrant configurations and other peculiarities of cancer morphology. This theory became the basis of microscopic diagnosis and also directed research into more functional considerations.

Specific Structural Pathology

Between 1820 and 1860, through the efforts of French clinicians, a long established system of clinical diagnoses based upon symptoms yielded to concepts of diseases, each related to localized structural pathology (instead of "inflammation of the chest," they recognized specific entities such as pleurisy, pneumonia, etc.). In cancer, the work of Müller and others between 1850 and 1870 made it possible to differentiate between benign and inflamed lesions and to recognize malignant growths in terms of both symptoms and lesions. It was thus possible to establish a group of clinically identifiable, malignant diseases, and the next step was to find the etiology of this disease called cancer.

Era of Experimental Research (1880 to present)

Predisposition

Virchow in 1858 proposed that the specific cause of cancer was both an irritation and a predisposition of the tissues. Thiersch's theory (1865) of senile disposition or growth-energy-imbalance proposed the idea that diminished stromic resistance occurs, whereby the actively proliferating epithelium is able to establish an advantage over the stroma, thus forming the nucleus of a neoplasm. Neither of these theories was altogether convincing at the time. Cohnheim's "embryonic rest" hypothesis was in reality the successor of earlier ideas of an undifferentiated blastema germinal layer as a source of cancer. He postulated that some defect originating in embryonic life became the focal point of tumor formation, a hypothesis which demands the existence of embryonal inclusions in man. These can be readily found, but there are many more that have not undergone malignant change than that have. For this reason alone, one must disregard this theory; yet a modicum of truth is based on the fact that numerous congenital tumors have been found.

Infectious Etiology

The infectious nature of cancer was first suggested in the 17th century but had to await the rise of bacteriology in the 1870s for the theory to be tested. The existence of a cancer microbe was postulated in 1872 and has been pursued ever since. In 1886, before the New York County Medical Society,[4] McNamara announced that clinical and experimental efforts had so far failed to link a bacterium with the cause of tumors, and tumors have never been successfully inoculated. Concerning the microbic source of carcinoma, he felt that the misplaced epithelial elements could account for all the reactive changes in the cells of the matrix. If a microorganism were to be considered the cause, why should it affect only the epithelial cells? There was no direct evidence at this time that pathogens could produce any more than reactive hyperplasias. The great advantage of proposing an infective origin to malignant processes was that it need not go beyond the organism and its cellular elements to explain the occurrence of malignant growth. In 1887, Scheurlen described a bacillus isolated from human carcinoma. He reported that culture-grown specimens of these organisms when inoculated into dogs produced epitheliomas in which the bacilli could again be isolated; but reappraisal by many other investigators concluded that bacilli were not directly involved in the production of tumors.

Viruses

The infection theory, however, continued to flourish after 1889 through reports of Russell's blastomycete-appearing fuchsin bodies in epitheliomas and Flexner's cellular inclusions in lymphosarcoma, which appeared to be protozoa. By the turn of the century, it was generally agreed by most investigators that cancer could result from an external or internal stimulus, probably a "potent living influence" such as a parasite,[14] and that its discovery would depend upon the adoption of very rigid research techniques. In 1901 Gaylord[15] reported the discovery in human cancer of undifferentiated parasites which, when inoculated into a guinea pig, produced adenocarcinomatous nodules. Preliminary evidence from these studies implicated the reactions of the protozoan inclusions in malignant tissue with those of vaccinia, the virus which by 1900 had been grown upon rabbit cornea. Gaylord's claim of finding the cause of cancer was discredited when attempts to reproduce it in other experimental animals failed. However, with the virus having been hypothesized and with the additional studies of Borrel in 1904 on contagious avian epithelioses, a new phase of the infection hypothesis began. Two Danes, Ellerman and Bang, reported the first tumor virus in 1908.[31,12] They were able to induce six successive passages of it in chickens, producing leukemia in each successive group. Yet this work was not convincing because at this time leukemia was not recognized as a neoplastic disease. In 1910, Peyton Rhous[12] described a malignant chicken sarcoma propagated by transplanting its cells and by their multiplication in the new host. One year later, these cells yielded a causative virus, termed the RSV virus, which has been maintained for more than 55 years in successive transplants.

Transplantation

The concept of cancer as a transmissible disease parallels the early popular beliefs of its contagiousness, found in many past reports of its transfer from one individual to another; the phenomenon of Cancer Houses, the concept of cancer as a plague in ancient days, and instances of its tranfer from patient to physician. Inoculations of human cancer into animals bore significantly on the question of parasite transmission during the 1870-1900 period. Among the efforts were those of two French investigators (Duplay and Cuzinin in 1892[4]) in which fragments of human tumors and those of spontaneous animal tumors were inoculated into a large group of different animals. Duplay and Cuzinin came up with only one positive result in dogs, which led them to question the validity of transplantation studies, especially those from man to animal and those between different animal species.

The priority for the first known successful tumor transplantation is credited to Novinsky who in 1875 succeeded in transplanting a nasal anaplastic tumor through two generations of dogs. In 1889, the first systematic survey of host-tumor relationship was made by Morau[4] who successfully transplanted through seventeen generations of mice a cylinder-cell epithelioma. Five years later he presented the following conclusions: (a) cylindrical epitheliomas of white mice are inoculable only in animals of the same species; (b) heredity plays a considerable role in the development of these neoplasms and prepares the soil for their evolution; (c) the neoplasms become generalized and this process is hastened by trauma; (d) gestation accelerates the evolution of these tumors; (e) neoplasms possess a variable virulence which may eventually lead to the death of the host; (f) neoplasms become progressively less inoculable and virulent in other hosts, provided they are of the same species; and (g) when these neoplasms are not ulcerated, they are devoid of bacteria.

Irritant Etiology

The essentials of the modern cell irritation theory are found in the previously considered views of Virchow and the role of environmental trauma first shown by Potts. The ocurrence of epithelial cancer among workers in the coal tar and paraffin industries was noted in 1875 and discussed from a clinico-theoretical point of view[3,35] with regard to the various carcinogenic effects of tars, roots and tobacco smoke. Among the first to attempt to produce experimental cancer with strictly irritative stimuli was Martin in 1882.[3,36] He administered injections of oil of sweet almonds converted into an irritant with the addition of croton oil, and he found that the animal developed a lung lesion corresponding to an epithelioma. Another investigator in 1889 painted preparations of gas and coal tar upon the skin, vulvae and nipples of dogs for months but managed to produce only local inflammatory changes.

By the turn of the century a number of researchers believed that external stimuli could induce an "anaplastic" process of the cell which involved no change in its position or relationship with neighboring cells. Around 1905, investigators using chemical stimuli showed that certain chemicals caused cellular proliferation but not neoplasms. The first true experimental production of cancer was by Fibiger in 1913 when he was able to feed rats a particular type of cockroach and later, at autopsy, found gastric papillomas and in some cases even carcinoma. In 1916, two Japanese investigators, Yamagiwa and Itchikawa, were able for the first time to initiate the production of a carcinoma with a chemical stimulus. They had applied coal tar two to three times a week to the internal surface of the rabbit's ear (spontaneous tumors had never been previously found there). Two to three months later, warty outgrowths covered with thickened, horny epithelium appeared in the painted area. Later, malignant change set in and infiltration and metastasis became apparent. This was the beginning of what today occupies the talents and time of many researchers working with experimental models, using chemical initiators, and then attempting by other means to reverse the early changes which appear.

Conclusion

Clinical observations, classification and theories of cancer have extended from the dawn of medical history and show that cancer was considered a systemic disease and that only visible cancer was treated. It was not until biological and pathological sciences came into their own in the 18th and 19th centuries that a scientific approach to neoplasms became feasible. Foundations of the present knowledge of oncology rest upon the compound microscope and its use in the study of normal and diseased tissues, facilitated by techniques of tissue preparation and staining. It was then shown that neoplastic diseases are characterized by an abnormal proliferation of cells, which refuse to obey the natural laws of growth. Men like Müller, Hunter, Cohnheim and Virchow were among the investigators of the 19th century whose labors led to the description of tumors, to the differential diagnosis based on biopsy and the course and prognosis of the specific neoplastic processes. So extensive were these studies that few fundamental additions have had to be made to the gross and microscopic studies of morphology.

Now, investigations into the basic cause and reversal of neoplastic mechanisms are our major concern.

James Krook, M.D.*
Minneapolis, Minnesota

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*Presently interning at Duke University Hospital, Durham, North Carolina.

On Headaches

Strong and continued headaches with fever, if any of the deadly symptoms be joined to them, are very fatal. But if without such symptoms the pain be prolonged beyond twenty days, a discharge of blood from the nose or some abscess in the inferior parts may be anticipated; but while the pain is recent, we may expect in like manner a discharge of blood from the nose, or a suppuration, especially if the pain be seated above the temples and forehead; but the hemorrhage is rather to be looked for in persons younger than thirty years, and the suppuration in more elderly persons.*

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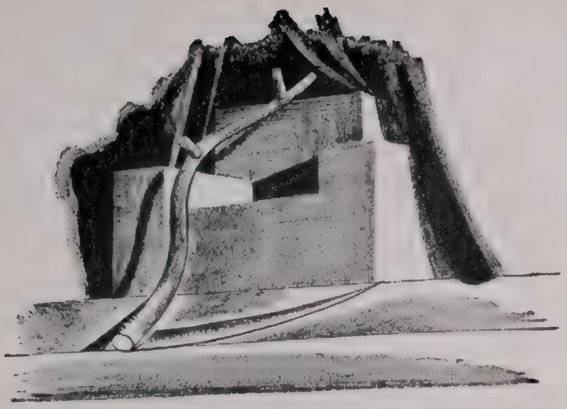
*Hippocrates: The Book of Prognostics.



In Memoriam

All that tread the globe are but a handful to the tribes that slumber in its bosom.—Bryant

ALBERT J. EMOND, M.D.

Dr. Albert J. Emond, 67, Farmington physician, died April 10. Born in Minneapolis, Dr. Emond obtained his medical degree at the University of Minnesota. He interned at the Charles T. Miller Hospital in St. Paul and practiced in Hankinson, North Dakota and Minneapolis before going to Farmington.

He was on the visiting staffs of St. Mary's and Fairview Hospitals in Minneapolis and a member of the Hennepin County Medical Society and the American Medical Association. Dr. Emond was an Associate Member of the Minnesota State Medical Association.

He is survived by his wife and son. Dr. Joseph S. Emond of Farmington is his brother.

GEORGE E. HUDSON, M.D.

Dr. George E. Hudson, 75, Minneapolis physician, died April 9. Born in Canada, Dr. Hudson, however, obtained his medical degree at Harvard University Medical School.

He was a member of the Hennepin County Medical Society and the American Medical Association and an Associate Member of the Minnesota State Medical Association.

He is survived by his son and two daughters.

ARTHUR I. ARNESON, M.D.

Dr. Arthur I. Arneson, 77, Morris surgeon, died April 10. Born in Emmons, he received his medical education at the University of Iowa, later moving to Austin where he practiced medicine there and in Starbuck.

Dr. Arneson was an enthusiastic fisherman, big game hunter and outdoors photographer. He was well-known for his interest and leadership in conservation activities, and his outdoor films were of such professional quality that he was called upon to show them before many sportsmen's groups.

He was a member of the Board of Directors of the Lakeland Mental Health Center, Fergus Falls, a member of the American Association of General Practitioners, the West Central Minnesota Medical Society, the American Medical Association and a 50 Club Member of the Minnesota State Medical Association. In 1965 Dr. Arneson was named recipient of the WCCO Radio "Good Neighbor Award," an honor bestowed upon persons who had contributed to an unusual degree to the betterment of their communities and the state.

Dr. Arneson is survived by his wife and two daughters.

HERBERT Z. GIFFIN, M.D.

Dr. Herbert Z. Giffin, 90, last survivor among a half-dozen doctors practicing with Doctors Will and Charles Mayo when they formed the Mayo Clinic, died April 25.

A native of Kirkwood, N. J., and a graduate of Johns Hopkins University, Dr. Giffin joined the Mayo group in 1906, serving as a specialist in diseases of the blood.

He was a member of the Zumbro Valley Medical Society, Southern Minnesota Medical Association, Minnesota Society of Internal Medicine, Minnesota Academy of Medicine, Central Interurban Clinical Club, Central Society for Clinical Research, American Medical Association, American Association for Advancement of Science, Association of American Physicians, American Society for Clinical Investment and a 50 Club and Life Member of the Minnesota State Medical Association. Dr. Griffin was a former president of the Minnesota State Medical Association and the winner of its distinguished service medal.

He is survived by his wife, two sons, and a daughter, Dr. Mary E. Griffin, of Winnetka, Illinois.

EARL ARTHUR SCHULTZ, M.D.

Dr. Earl A. Schultz, 45, died in Mt. Sinai Medical Center in Los Angeles, California, April 26. Born in Winnipeg, Canada, Dr. Schultz was a graduate of the Faculty of Medicine, University of Manitoba, Winnipeg. His post-graduate work in anesthesiology was done at the University of Minnesota Hospitals.

He was a member of the Hennepin County Medical Society, certified by the American Board of Anesthesiology, a member of the University of Minnesota faculty, member of the American Medical Association and the Minnesota State Medical Association.

He is survived by his sister.

WILLIAM F. MC MANUS, M.D.

Dr. William McManus, 55, practicing physician in Princeton since 1946, died February 23, in Albuquerque, New Mexico. The family had moved to New Mexico last October.

A graduate of Loyola University in Chicago, he received the Blue Key Honor and a teaching fellowship, upon completion of his post-graduate work. He was a member of the American Medical Association, West Central Minnesota Medical Society and the Minnesota State Medical Association. Dr. McManus founded the McManus Clinic in Princeton.

He is survived by his wife and children.

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Warnings: Use only after critical appraisal in patients with liver damage, renal damage, urinary obstruction or blood dyscrasias. If toxic or hypersensitivity reactions or blood dyscrasias occur, discontinue therapy. In closely intermittent or prolonged therapy, blood counts and liver and kidney function tests should be performed.

Precautions: Observe usual sulfonamide therapy precautions including maintenance of an adequate fluid intake. Use with caution in patients with histories of allergies and/or asthma. Patients with impaired renal function should be followed closely since renal impairment may cause excessive drug accumulation. Occasional failures may occur due to resistant microorganisms. Not effective in virus and rickettsial infections.

Adverse Reactions: Headache, nausea, vomiting, urticaria, diarrhea, hepatitis, pancreatitis, blood dyscrasias, neuropathy, drug fever, skin rash, Stevens-Johnson syndrome, injection of the conjunctiva and sclera, petechiae, purpura, hematuria or crystalluria may occur, in which case the dosage should be decreased or the drug withdrawn.

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Eli Lilly and Company

Eli Lilly and Company announced a change in the dosage form of Ilosone Liquid (erythromycin estolate). This new preparation provides 250 milligrams per 5 cc teaspoonful, twice the dosage strength of the preparation which was first offered in 1967.

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And tell, although she isn't bid,
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*Richard Armour: The Medical Muse, 1963.

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Toxicity in Cancer Chemotherapy

(For Answers Dial for Tape #16)

1. What are the 4 steps in combatting the nausea, vomiting and diarrhea which are side effects of many drugs used in cancer chemotherapy?
2. Two simple remedies may help in the management of stomatitis. They are:
   a) avoidance of................
   b) administration of............
3. When handling a patient who is receiving chemotherapy the W.B.C. should be performed at regular intervals. What should be done if the count:
   a) drops below 3,000/mm^3 ?
   b) drops below 2,000/mm^3 ?
4. What is the management of post-chemotherapeutic thrombocytopenia with ecchymoses?
5. What is the prognosis of alopecia following cancer chemotherapy?

Tetanus Prophylaxis

(For Answers Dial for Tape #21)

1. Burns are an indication for tetanus antiserum. True or False?
2. Under what circumstances is the administration of 0.5 ml tetanus toxoid *adequate* prophylaxis following a severe injury in a street accident?
3. What antibiotics are effective in the prevention of tetanus?
4. What is the only remaining indication for equine tetanus antitoxin?

Congestive Heart Failure in Infants

(For Answers Dial for Tape #43)

1. The incidence of congenital abnormality of the heart in the newborn is: a) 0.006% b) 0.06% c) 0.6%
2. The mortality in infants with congenital heart disease developing congestive failure under one month of age is: a) 20% b) 40% c) 60% d) 80%
3. There are 4 cardinal symptoms of congestive heart failure in infancy. Which of these is related to pulmonary venous pressure?
4. The digitalizing dose of Digoxin is calculated on the basis of weight. The usual dose in mgms/Kg body weight is: a) 0.008 mgms b) 0.08 mgms c) 0.8 mgms

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Minnesota Medicine at a Glance

Anuria Secondary to Ethylene Glycol Intoxication—*Smith et al.* Page 1049

Ethylene glycol intoxication usually causes death by kidney damage which is reversible. An alcoholic male entered the hospital after four days of anuria; ethylene glycol intoxication was diagnosed by a finding of calcium oxalate crystals in renal biopsy. He survived after treatment with peritoneal dialysis and hemodialysis.

Vascular Compression of the Distal Duodenum—*Imes* Page 1055

The symptomatic compression of the third portion of the duodenum by the root of the mesentery may occur more frequently than is now commonly diagnosed. The author reports 11 cases discovered while doing 1643 upper gastrointestinal x-ray examinations over a 14-month period. The anatomic basis, the symptoms, the diagnostic x-ray findings, and the treatment are discussed.

Congenital Pseudarthrosis of the Ulna—*Shertzer et al.* Page 1061

Two cases of an interesting orthopedic anomaly are discussed, illustrating the progressiveness of the condition if left untreated and the difficulties in its correction.

Hospital-Acquired Infections—*Oh et al.* Page 1067

Hospital-acquired infections during a six-month period, January through June 1967, on six surgical stations were analyzed. The overall infection rate was 5.2%. *Staphylococcus aureus* accounted for more infections than any other single bacterial species. However, enteric gram-negative bacteria accounted for more than one third of the hospital-acquired infections.

The antibiotic therapy prior to documentation of hospital-acquired infection was reviewed. Infection with gram-negative bacteria occurred with nearly equal frequency in patients being treated with antibiotics as in those not receiving antibiotics. Hospital-acquired infections with gram-negative enteric bacteria were most frequently found in patients receiving broad spectrum antibiotics.

Giardia lamblia as Parasite in Humans—*Mears and Zinneman* Page 1107

Giardia lamblia is found in human stool all over the world, even in the United States. Three cases from the Minneapolis Veterans Hospital are reported. It is associated with diarrhea, other gastrointestinal symptoms, nervousness and anemia but there is a question of pathogenicity. The history of the discovery and the life cycle of the parasite is discussed.

Cholecystocolonic Fistula—*Snider and Judd* Page 1141

A 20-year review of cholecystocolonic fiistulas seen at the Mayo Clinic is presented along with a detailed case report.

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AUGUST, 1969

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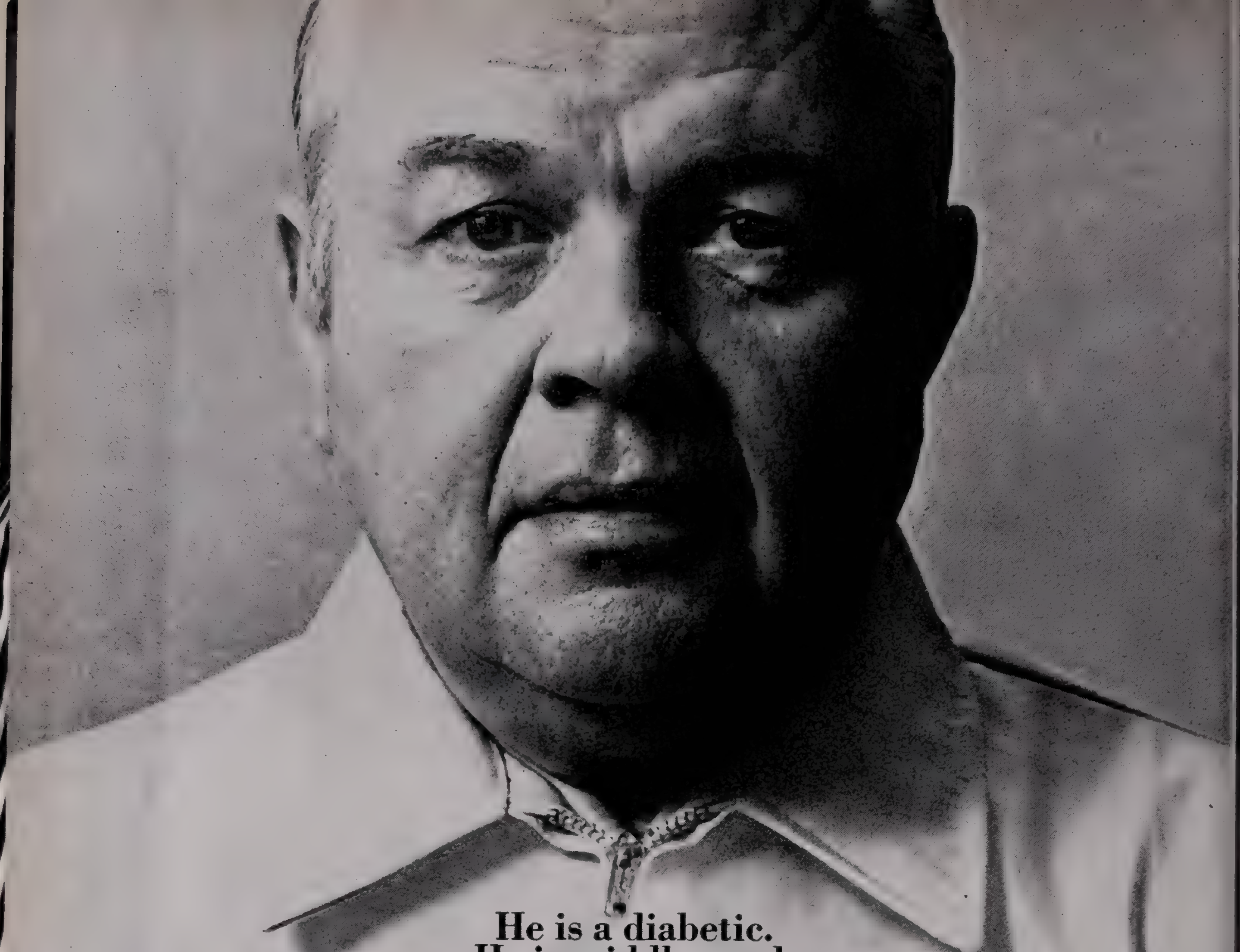

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Precautions: Overgrowth of nonsusceptible organisms may occur. Con
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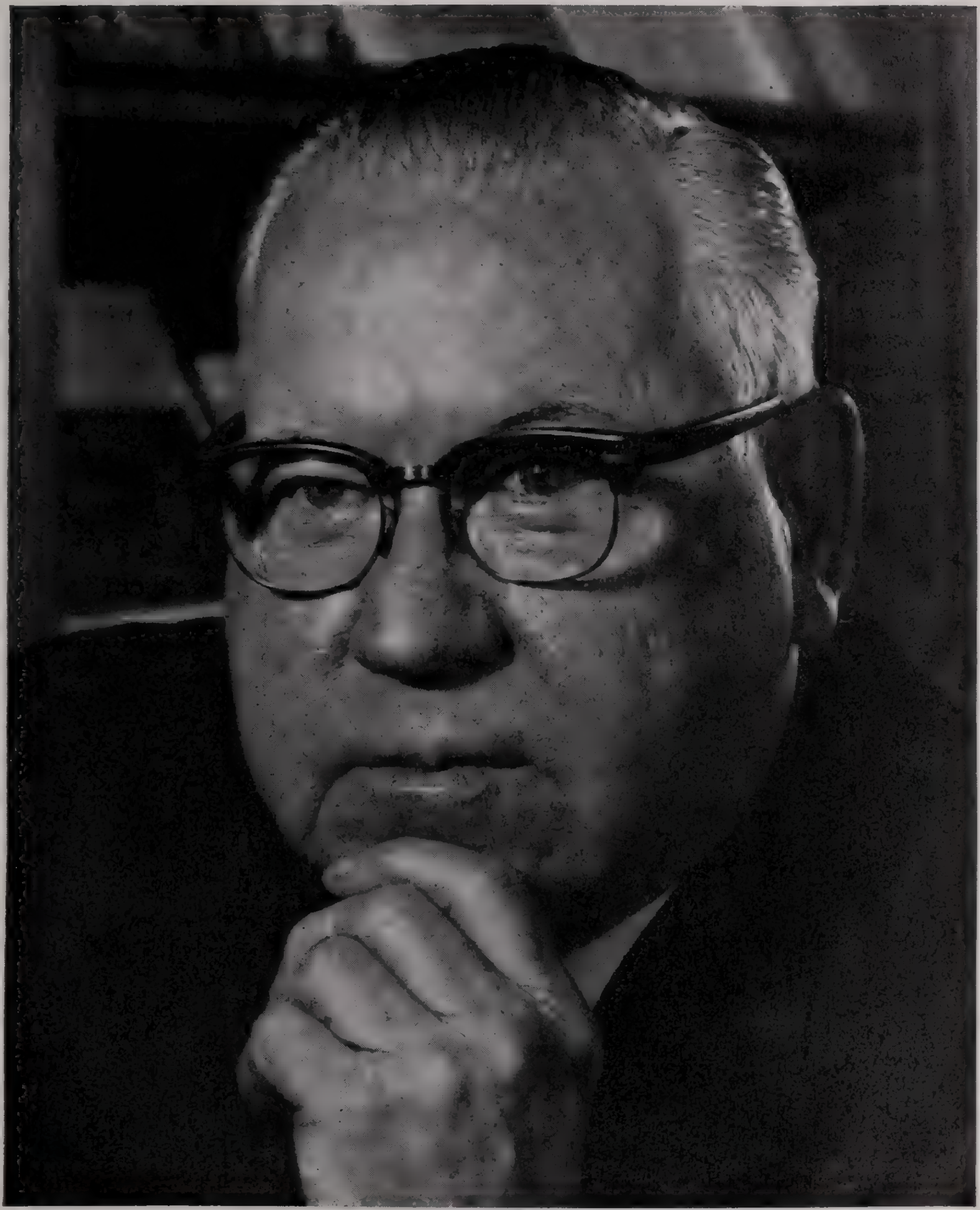

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Minnesota State Medical Association

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See the President's Letter, Page 1177.

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President's Letter

THROUGHOUT MOST of recorded history, man has extolled the heart as the seat of the mind and the soul both in music and verse. The "heart" over the centuries has played an important part in our daily lives, as witness the numerous familiar expressions which have accumulated over the ages. No less a scholar than Aristotle proclaimed the heart as the seat of intelligence. In this issue of MINNESOTA MEDICINE, we are proud to give you a more scientific slant on the heart as it really is.

The Minnesota Symposium on Prevention in Cardiology contained in this special issue of MINNESOTA MEDICINE is *must* reading for all physicians regardless of specialty training or interests. Most doctors have a deep interest in cardiovascular disease and especially coronary thrombosis because of its high incidence in physicians. We doctors have a self-interest in the causes of heart disease; likewise we are constantly seeking to learn more of the methods to prevent heart attacks. This special issue therefore is an excellent review for all of us as well as a means of updating our knowledge in this field. The authors and contributors are to be highly complimented for this excellent and rewarding symposium.

For more than a decade and a half, cholesterol has been incriminated in the minds of many researchers as the principle cause of coronary thrombosis as against heredity, obesity, stress, to mention only a few of the many possible contributors to coronary heart disease. This symposium puts cholesterol in better perspective in relationship to coronary thrombosis. Serum lipid fractions, saturated and unsaturated fats, diets, hyperlipidemia, obesity, elevated blood sugar, hypertension, cigarette smoking, physical inactivity and exercise are all covered in depth in this series and make most interesting reading.

To become a quasi-authority on the prevention of cardiac disease don't miss studying this issue of MINNESOTA MEDICINE. If you want to learn how to improve and protect your own heart and blood vessels, do likewise.

We are constantly bombarded by almost every one about the need for more physicians, expanding medical school admissions and building more medical schools. It may be that *Prevention of Coronary Thrombosis in Physicians* would help the doctor shortage a mite.

I would also like to take this opportunity to call to your attention the September issue of MINNESOTA MEDICINE as additional *must* reading. This special issue will contain papers on Chronic Respiratory Disease in Children and Adolescents. These papers are taken from a Continuation Course on Chronic Respiratory Disease held at the University of Minnesota in September of 1968. Those selected are most interesting and informative as well as most practical, providing right up-to-date knowledge on Respiratory Disease. The authors are to be congratulated on these excellent papers.

So let's get educated on heart attacks and lung disease.

Delmar R. Gillespie

Delmar R. Gillespie, M.D.
President
Minnesota State Medical Association

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minnesota medicine

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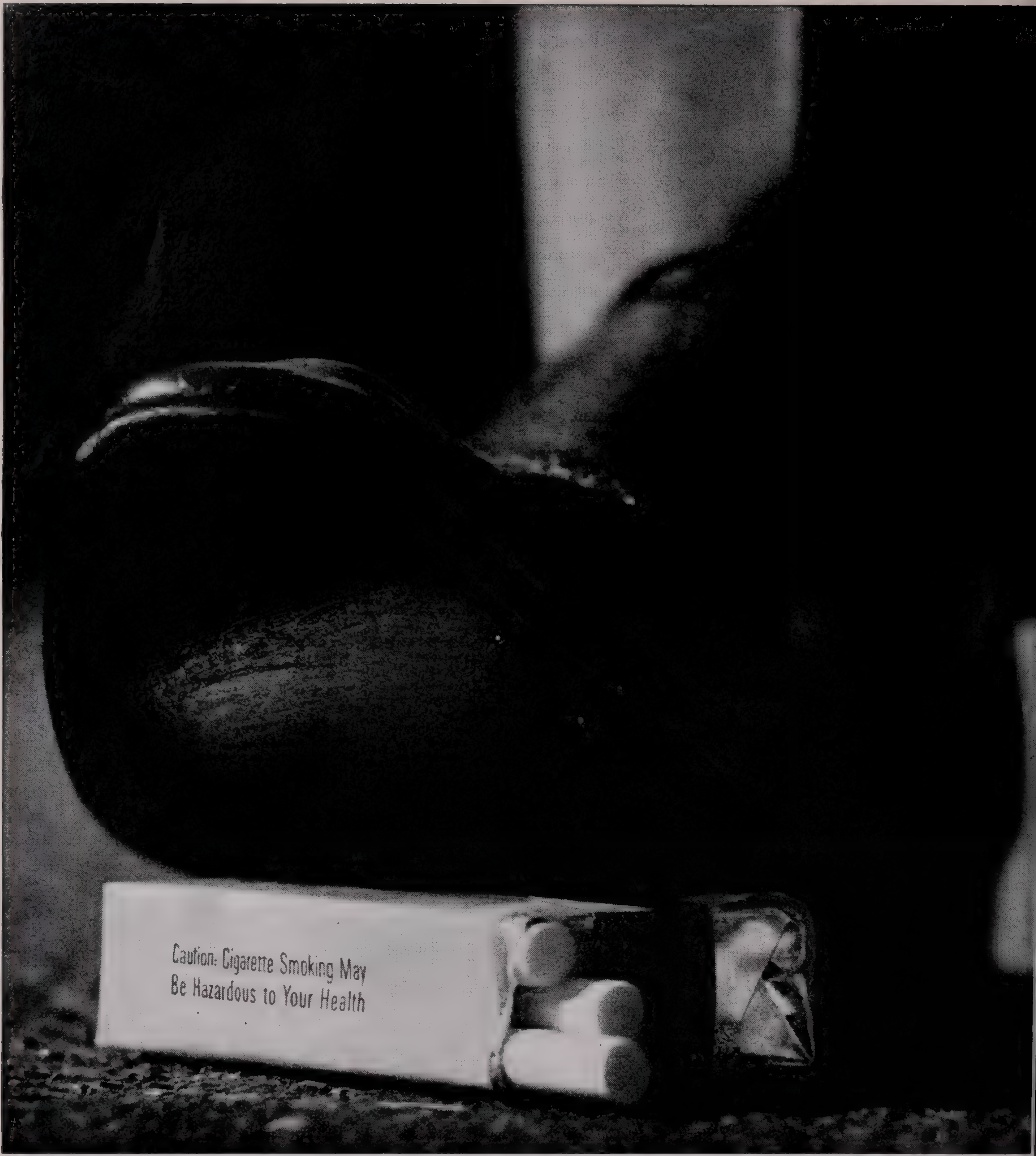
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THE MINNESOTA SYMPOSIUM
ON
PREVENTION IN CARDIOLOGY

Reducing the Risk of Coronary And Hypertensive Disease

Edited by:
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and
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Sponsored by:
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May 2-3, 1968

Heritage Hall, Kahler Hotel
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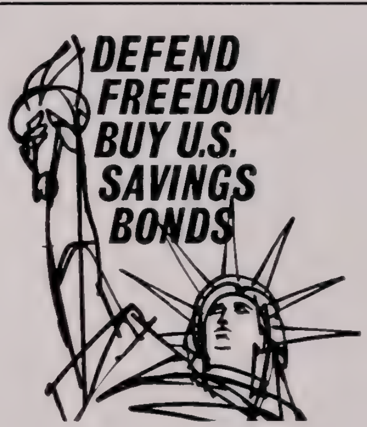
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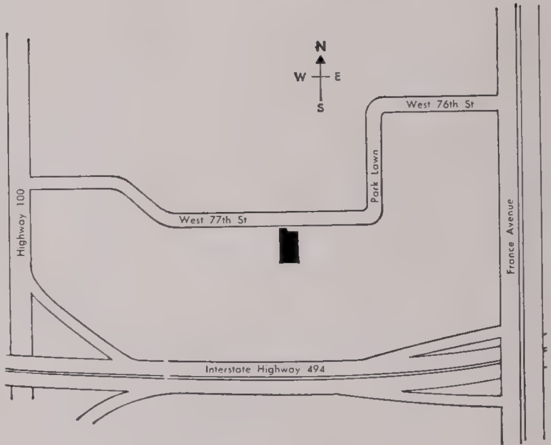
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Welcome

Ladies and gentlemen, good morning. It is my very pleasant responsibility to welcome you to Minnesota, to Rochester, and to the Mayo institutions. At a time when coronary heart disease has reached epidemic proportions in the western world, it is particularly appropriate to spread the gospel of preventive medicine and to disseminate all available information about reducing the risks of atherosclerosis. We are beyond the stage when this type of information can be regarded as of interest only to the epidemiologist or the clinical investigator. It must be made available to, and used by, the medical practitioner who now spends his time almost exclusively with diagnosis and treatment rather than prevention. And that is what this symposium is all about.

The Minnesota Heart Association is proud to be a cosponsor of this symposium on prevention in cardiology. Dr. Henry Blackburn, chairman of our association's Professional Education Committee, deserves great credit for organizing the program and assembling the distinguished participants from this country and abroad. Others who have worked on the local arrangements are Drs. Kenneth G. Berge, Stewart L. Nunn, and John A. Spittell, Jr. With a "Thank you" to these gentlemen, I once more bid you "Welcome" and turn the podium over to Dr. Henry Blackburn.

John L. Juergens, M.D.*
Rochester, Minnesota

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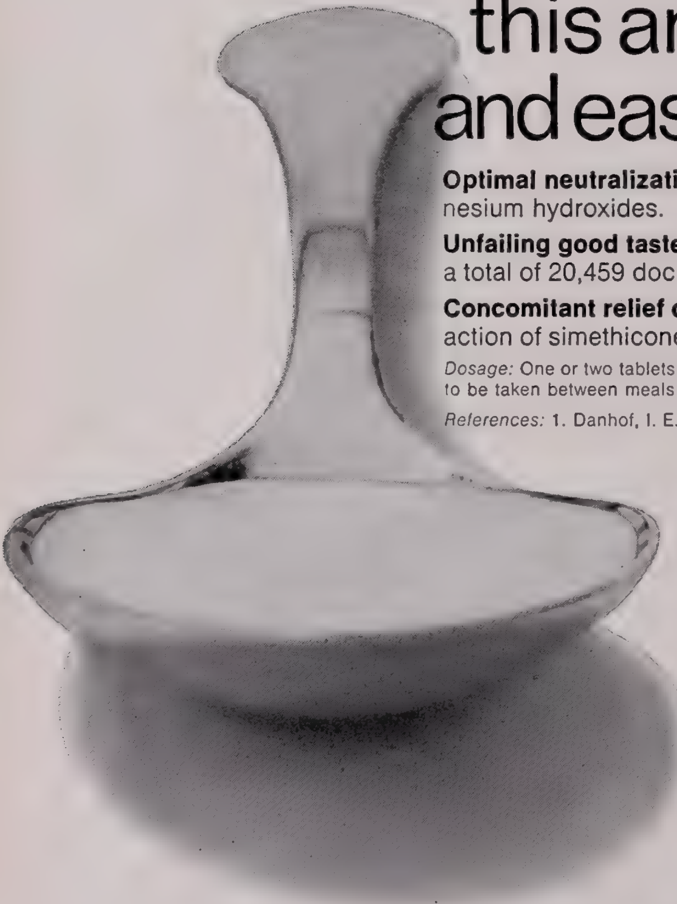
*Former President, Minnesota Heart Association. Associate Professor of Medicine, Mayo Graduate School of Medicine (University of Minnesota), and Consultant, Section of Medicine, Mayo Clinic, Rochester.



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Introduction*

THE ANALOGY is far from perfect, but I like to think of the development of the epidemiological study of cardiovascular diseases as occurring in Classical, Romantic and Modern periods, like those of serious music. The Classical Period provided an important base, with classic epidemiological compilation and study of International Vital Statistics on Causes of Death. The apparent national differences found in cardiovascular mortality gave an initial impetus to, and clues for, further study. The Romantic Period was one in which a few distinguished physicians and scientists, led by Paul Dudley White and Ancel Keys, made their peripatetic rounds in many varied and exotic places. They obtained important clinical impressions of cultural differences in the frequency of cardiovascular diseases and focused world-wide attention on the great implications of such differences. The Modern Period is characterized by systematic and long-term studies of cardiovascular manifestations in natural populations, measurement of personal characteristics, and active experimental intervention on factors of risk.

Follow-up study of apparently healthy persons has led to estimates of future risk of coronary attack, based on measurement of predisease attributes. The relative importance of these factors and their interaction are now being elucidated. Here, today, the means and the effects of modifying factors of risk will engage us.

The time is appropriate for a call to greater investigation into the possibilities of prevention of cardiovascular diseases and the wider application of current knowledge in attempts to reduce their toll. It is appropriate to sound this call in Minnesota, where so many have been concerned with preventive cardiology, and in Rochester, where the Mayo Clinic holds the respect of all for its practice of diagnostic and therapeutic medicine.

We are most grateful for the pleasant host arrangements in this quiet, single-minded medical community. We owe these arrangements, and the gracious hospitality of the Clinic, to Kenneth Berge and John Spittell, Stewart Nunn and John Juergens, as well as to Helen Bies of the Minnesota Heart Association. The Mayo Clinic and Foundation, and the staff of the Minnesota Heart Association, are available to assist you.

We are pleased now to introduce a distinguished faculty, one which has the richest experience available in the evaluation and attempted reduction of the risk of coronary and hypertensive disease.

Paul Dudley White of Boston, and of the World at Large, once stood alone with a depth of clinical knowledge and a remarkable breadth of understanding of heart diseases. Because he stood strong and with curiosity, vision, and diplomacy, he no longer stands alone but is rather conjoined in a large and important medical enterprise, Preventive Cardiology. Each of us here owes him a professional debt for our own emerging understanding of the distribution, causes, and control of heart diseases. Many more people will come to owe their well-being to Paul White. This is because he so effectively raised the professional challenge of prevention in cardiology and because he provides such a personal challenge to all for living more balanced lives.

Henry Blackburn, M.D.†
Minneapolis, Minnesota

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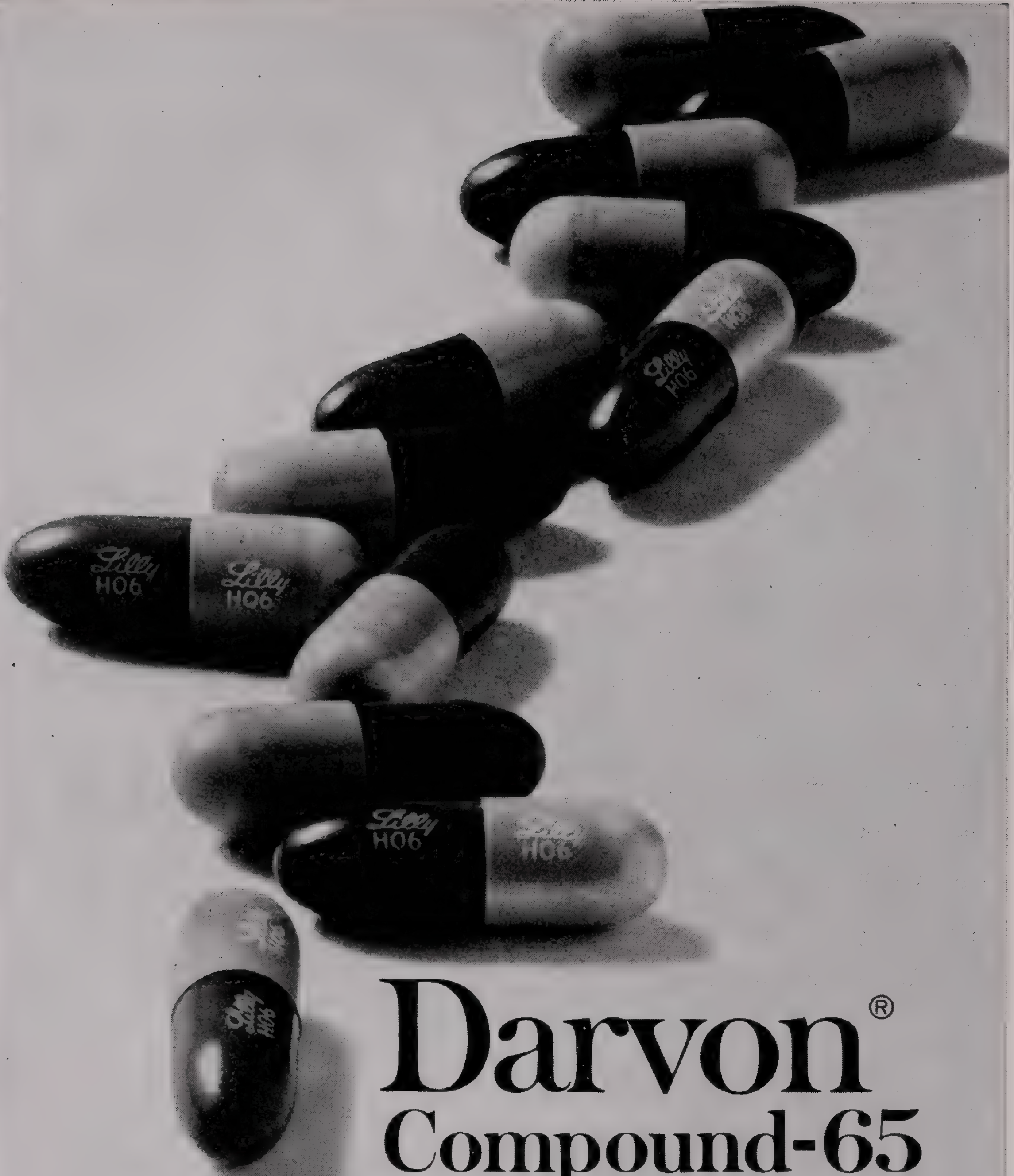
*Presented at the Minnesota Symposium on Prevention in Cardiology, May 2-3, 1968 in Rochester, Minnesota.

†Professor, Laboratory of Physiological Hygiene, University of Minnesota.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|| Cardiology*

The Challenge of Prevention

PAUL DUDLEY WHITE, M.D.
Boston, Massachusetts

IT IS MY FUNCTION to set the stage for this symposium historically, and perhaps romantically, and to outline some of the major problems of the challenge.

We have doubtless always had cardiovascular diseases and much the same kinds or etiologic types that we have today, but also in all probability in different total prevalence and relative incidence. We can do little but guess how common heart disease was in toto or in each separate kind before the days of autopsies. However, in the Bible and especially in the writings of Pliny the Elder sudden deaths were recorded which were instantaneous enough to have been due to coronary insufficiency and ventricular fibrillation. At other times there were recorded more slowly evolving deaths due quite likely to myocardial infarction.

With the descriptions of post-mortem examinations in the sixteenth and seventeenth centuries we find other cardiovascular diseases identified, especially infected and deformed heart valves, enlarged atria and ventricles, aortic aneurysm, and pericarditis. In the eighteenth century congenital lesions and coronary disease were described, as well as the symptom of angina pectoris and the signs and symptoms of heart failure. Another century went by, however, before hypertensive heart disease came into its own as an important and quite common type.

Heart Disease in the Twenties

When I was a very young doctor we were still in the dark ages; then in the 1920s we began to move ahead trying to learn the overall prevalence of cardiovascular disease and the incidence of the various types.

Infectious Heart Involvement

Rheumatic heart involvement, both acute and chronic, made up about half of all our cases. Syphilis and aortic aneurysms were still common, and hypertension ranked second as an etiological type. Diphtheria was still a potent threat to the myocardium.

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*Presented at the Minnesota Symposium on Prevention in Cardiology, May 2-3, 1968 in Rochester, Minnesota.

The Electrocardiogram

Clinically significant atherosclerosis of the coronary arteries was low on the list, although we had become acquainted with its diagnosis both symptomatically and objectively, especially with the help of the electrocardiogram. Relatively rare in our figures were congenital heart patients who infrequently sought help because none was available. A statistical study by Duckett Jones and myself in the 1920s noted the incidence of congenital cardiovascular defects as 1.5 per cent, while 25 years later in a similar study we found it responsible for 7.9 per cent of 3,000 so-called cardiacs. There were also 3.0 per cent thyrocardiacs, now rarely seen.

Heart Disease in the Sixties

We have made considerable strides, sometimes fortuitously, in the reduction of the prevalence, incidence, and mortality from the infectious types of heart disease, especially the rheumatic, which has dropped far down the scale, though it still exists, especially in parts of the world where preventive measures are few or nil, as in some parts of Central Africa where one sometimes sees tight mitral stenosis in children.

Other infectious types have also been controlled in large part: diphtheria, syphilis, and subacute bacterial endocarditis. Hypertension of certain recognized etiologies and even "essential" hypertension have declined a good deal in the mortality column, under medical treatment.

This leaves two major causes of cardiovascular disease almost untouched, at least so far as their prevention is concerned: congenital heart disease and coronary heart disease. In this program we are concerned with coronary heart disease, but I hope that when we know more about genetics and pay more attention to the health of the human fetus, and even before we have reduced in major degree both the prevalence and the mortality of coronary heart disease, especially in young and middle aged males, we may begin to plan more of an attack on congenital defects. These may eventually constitute our major cardiovascular challenge.

We must now concentrate on atherosclerotic and thrombotic disease, not only of the coronaries but also of the aorta, the cerebral and renal arteries, and those to the legs, for it is the same process which affects them all: both sclerotic and thrombotic.

Coronary Heart Disease

Why is there a greater challenge now than when I was a young cardiologist nearly 50 years ago? Let me list five of the various reasons for our concern:

Prevalence of the Disease

There has been an increasing prevalence of coronary disease as well as an increased incidence. Austin Flint in 1866 and Osler in 1892 called angina pectoris rare, and they knew the symptom well. I am quite sure that I was as able to determine by careful history in the 1920s as I am in the 1960s the presence of symptoms and signs of the disease, including the diagnosis of angina pectoris, and to recognize the electrocardiographic abnormalities and the collateral signs of acute myocardial infarction long before coronary angiography. I was specializing in the whole field of cardiology as I am now and seeing the same number of, or somewhat more, cardiacs, both new and old. In 1924 it took me two years to see 100 new patients with coronary heart disease in contrast to one year in 1965.

A careful scrutiny of my own ward patients in 1912 and 1913, before we had an electrocardiograph, has revealed very few cases of angina pectoris, and only one case of myocardial infarction found at autopsy. I have also looked over electrocardiographic glass plates of the first hundred of our patients in 1914 and found only one case with typical acute myocardial infarction and one with complete heart block. Another clue to the relative infrequency of coronary heart disease as a clinical problem compared to other subjects like rheumatic heart disease was that in the first 100 of my published papers only two concerned coronary heart disease, whereas from 1946 to 1957 inclusive there were 21 such papers out of 99 publications.

The Age of the Coronary Patient

We all have had the experience that of late we have been seeing younger and younger males with coronary heart disease. This was strongly supported by a report by Samuel Levine, who analyzed in 40 families the age of onset of angina pectoris in father and son. He found that the sons began having angina 13 years younger than had their fathers and that their deaths also occurred at a younger age. This fits in with my own experience. I have compared the ages of 100 new patients seen between 1924 to 1926 with those of 100 similar cases seen between 1964 to 1965. There were 5 per cent in the 1960s under the age of 40 compared to 1 per cent in the 1920s, and 21 cases under 50 in the later group compared to seven in the earlier. It was Sam Levine's belief, as it is mine, that something has happened in the last generation which may explain these differences.

Sex

One hundred years ago the wife in the U.S.A. outlived her husband by about one and a half years, but now this advantage has changed to an average of six years. It is clear that atherosclerosis and thrombosis of the coronary cerebral arteries and aorta are responsible, in the main, for this difference. The longevity of the husband must be increased to match, so far as possible, that of his wife. It may be that a shorter male life is a law of nature, but some improvement at least should be possible. In the series of 100 new cases of coronary heart disease of my own there were 72 men and 28 women; of the 21 patients under 50 years of age, 19 were men and only two were women; of the five cases under 40, all were male. In two separate series of 100 cases under the age of 40 years, studied years ago by Sam Levine and myself, 193 were men and only seven were women.

Heredity

How much of the responsibility is to be credited to the genes and how much to the environment is not known. It is possible that the relative responsibility of these factors may vary from family to family and from person to person. Studies of a few thousand coronary-ridden families might determine what changes in their environment would improve their longevity and health.

Occupation

Years ago when I was a young doctor we had a good many real laborers in this country. Most of their hearts were sound, unless they had had rheumatic fever or syphilis, but I recall that their radial arteries were beaded. It was the affluent white collar executive and capitalist who occasionally had coronary heart disease then. Now the situation seems to be reversed. The 'laborer' no longer labors but owns an automobile and gets the richest cuts of beef and puts on pounds of weight; in middle age his coronary arteries become beaded and occluded while his radial arteries remain smooth.

Meanwhile the executive has become wiser and, with the help of his wiser doctor, tries to keep physically fit and is beginning to benefit. Incidentally, I have been trying to persuade groups of young people in this country and overseas to rebel not against their parents but against their parents' bad habits. Sometimes I am viewed with concern as a Don Quixote sparring with windmills; but my experience over a long life in seeing and following up a great many patients makes me believe that the next generation may benefit from our efforts, though it may be difficult to rehabilitate the fathers, even with transplants.

Smoking

A custom loathsome to the eye, harmful to the brain, dangerous to the lungs, and in the black stinking fume thereof, nearest resembling the horrible Stygian smoke of the pit that is bottomless.—James I of England

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Our models are lenses, coloring the world with as many different hues.—Emerson

The Wages of Excess

"Surely, kings must think that their stomachs are not made like other men's."

These were the rueful words of Luis de Quijada, Chamberlain to Holy Roman Emperor Charles V—commenting on his master's gluttony.

Disabling, agonizing gout attended the monarch's excessive gourmandizing—whether retributive in nature or merely correlative, who can say categorically! His biographer mentions "the highly-spiced dishes, the disgusting sausages, the forbidden fish, the early morning draughts of ale which had been placed outside the window for the frosty night to cool," and gives the following staggering catalogue of Charles' consumption for one day.

"The five o'clock beer was followed by a bowl of chicken broth, improved by milk, sugar and spices. At midday he ate a heavy dinner—roast mutton, for instance, succeeding large slices of beef, followed in turn by braised hare, and that by chicken—all being bolted, for he could not chew. After Vespers he would take a hasty snack, while midnight closed upon a substantial supper. When an Italian doctor warned him that he must give up beer, he flatly answered that he would not."*

No less than eleven periodic attacks of gout—the fifth one of quadruple dimensions—punctuated the Emperor's strenuous reign (1519-1556), descending suddenly to incapacitate their victim at critical junctures: a diplomatic confrontation, an Imperial Diet, a Papal conference, a Cortes session, a military enterprise. For in his vainglorious but doomed dream of unifying a fragmenting Empire, Charles was always on the move, traveling hither and yon throughout his vast dominions in response to political, religious, and military challenges.

With each attack of gout he had to either postpone or abandon his immediate objective and become virtually immobilized until he improved sufficiently to continue his royal expedition. Sometimes, in his later years, he had to be carried on a litter, which he insisted be an open one so that people could see that he was alive. During each attack he curbed his appetite—either by necessity or as a gesture of compliance toward his doctors. But after he recovered he flouted their orders and resumed his gargantuan consumption of food and drink.

While gout constituted Charles' major nemesis there were also numerous other chronic maladies of long standing: erysipelas, trauma from a fall off a horse, asthma, insomnia, general exhaustion.

Eventually he was obliged to capitulate to shattered health when he was stricken at Brussels by something he himself designated as "not gout" and his biographer fails to identify—except that it involved "fever." So, having failed to achieve his magnificent obsession of political consolidation and religious union for his Empire, Charles abdicated—to live another two years in retirement—without, however, renouncing his ravenous appetite.

Editor's Note: How does the student of human nature account for such paradoxicality as Charles' life illustrates? Why did his prodigious determination, herculean endurance, and invincible spirit in pursuing an ever-fading dream not deter him from the grossest self-indulgence? Perhaps psychologists can provide a glib answer. But answers come too easy! For who can really probe the deep dark intricacies of another man's soul!

---

*Edward Armstrong: The Emperor Charles V, 1902.

|| Cardiology*

The Essentiality of Prevention

ANCEL KEYS, Ph.D.†
Minneapolis, Minnesota

FOR SEVERAL DECADES we and the general public have been congratulating ourselves on "the spectacular advances of medical science" and "the miracles of modern medicine." There is much, indeed, to rejoice about in all fields of medicine, including cardiology.

For the rheumatic heart patient there are antibiotics against infection, drugs to suppress progressive damage, and finally surgical repair. For the congenital heart patient there is vastly improved diagnosis and the surgeon's new ability to patch up the mistakes of development. The hypertensive heart patient has drugs to lower his blood pressure; the cor pulmonale patient can at least be made less miserable for a while. For the coronary patient there are anticoagulants and intensive care units. For all cardiacs there are defibrillators and cardiac pacers and drugs to combat arrhythmias and failure. Finally, when all else fails, we look at Dr. Blaiberg walking around with his new heart and we read a forecast that before long a thousand teams of surgeons may be busy installing nuclear-powered contraptions to replace hearts diseased beyond redemption.

Prevention

In spite of all advances in diagnosis and treatment, prevention is essential for any real control over most of the heart disease problem.

No Miracles

Not only is prevention always better than cure, but for most of the victims of heart disease there can be good, sometimes remarkable success: management but no cure. Some congenital and rheumatic-fever heart patients

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*Presented at the Minnesota Symposium on Prevention in Cardiology, May 2-3, 1968 in Rochester, Minnesota.

Data cited here were obtained with help grants in aid from the U.S. Public Health Service (HE 04697, HE 04997, HE 04754, HE 04774), from the American Heart Association, New York, from the California State Olive Advisory Board, and many other sources to be acknowledged in later fuller publication.

†Professor and Director, Laboratory of Physiological Hygiene, University of Minnesota.

can be actually "cured" by surgery; some hypertensive hearts may be made nearly normal by treatment of the basic high blood pressure; but even if all such congenital, rheumatic fever and hypertensive patients had the most successful treatment, most of the heart disease problem would remain. Coronary heart disease makes up the bulk of this great remaining burden.

Prevention Is Possible

There is no dissent from the proposition that prevention is desirable, but it is instructive to consider some data on life expectation that indicate the poor net outcome of therapeutic advances. The most spectacular improvements in diagnosis and treatment have come since World War II. Table 1 shows the life expectation of white persons in the United States. At the end of the 1940s, 40-year-old men had an average life expectation of 31.2 years; 15 years later the figure was 31.7 years. Women aged 40 did better: at the end of the 1940s their expectation was 4.4 years longer than that of men, and 15 years later their advantage had advanced to 5.8 years. The net improvement in life expectation after age 40 from all medical advances has been appreciable for women, negligible for men.

TABLE 1

Life Expectation of White Persons Aged 40 in the United States

	Years Remaining	
Period	Men	Women
1949-51	31.2	35.6
1959-61	31.7	37.1
1965	31.7	37.5
Gain, 1950 to 1965	0.5	1.9

Incidence of Death

Consideration of the causes of death (Table 2) explains much. For white men aged 40 to 59 the death rate from all causes fell by only 7 per cent over these years; for women of the same age the improvement was 16 per cent, so that now their total death rate is less than half that of men. For the men the death rate ascribed to coronary heart disease *increased* by over 11 per cent; the coronary rate for women did not change. For American men coronary heart disease nullified much of the improvement in deaths from other causes registered since World War II. Perhaps some of this picture reflects change in diagnosis but, if so, why the difference between men and women? In any case, there is no indication that advances in diagnosis and treatment are improving the general coronary mortality picture.

TABLE 2

Death Rates, Per 100,000, Among U.S. White Persons Aged 40-59, Age Standardized

Year	Cause	Men	Women
1950	Coronary heart disease	327	78
1965	Coronary heart disease	364	77
1950	All other causes	699	493
1965	All other causes	591	400

Influencing Factors

Coronary care units are too new to have had any impact on national vital statistics, but reasonably acceptable estimates of the potential benefit can be made from information on the ordinary natural history of heart attacks and the mortality experience in special coronary units.

Coronary Care Units

Table 3 summarizes the general mortality experience with myocardial infarction in the absence of special coronary care units. Roughly one out of seven or eight patients dies suddenly, often within a few minutes of the first symptom. During the next three to four weeks, corresponding to the period of acute illness in the hospital, some 20 per cent will die. In the next eleven months the mortality adds up to become similar to that in the first hours. As a result, among persons who have a heart attack, half are dead within a year.

TABLE 3

Prognosis of Heart Attacks. (See 1963 Acta Med. Scand., Suppl. No. 406)

	Per Cent Who Die	
Period	First Attack	Recurrent
Under 2 hours	13%	15%
2 hours-4 weeks	20	22
4 weeks-1 year	13	15
One year mortality	46%	52%

Table 3 gives the picture in the absence of coronary care units. So we now ask: What happens in such units? The experience in coronary care units is that, during the period the patients are in the units, the death rate is reduced some 20 to 40 per cent below the usual experience. Accordingly, the overall effect of such units on the one-year mortality can be summed up in Table 4. The most optimistic estimate is that the one-year mortality might be reduced from 50 to 41 per cent. There is no doubt at all that some coronary patients who would die otherwise are temporarily saved by the prompt application of emergency measures in the coronary care unit. But there also can be no doubt that the provision of first-class coronary care units in every general hospital in the nation would not greatly change the total coronary mortality picture.

TABLE 4

Estimation of the Potential Life-saving Effect of Special Coronary Care Units Measured in Terms of One-Year Mortality Among 100 Persons Suffering Heart Attacks

Period	Number of Deaths	
	No Unit	With Unit
Under 2 hours	14	12*
2 hours-4 weeks	21	14
4 weeks-1 year	15	15†
	—	—
One year mortality	50	41

*Assuming more speedy admission than is now the rule.

†Assuming that patients saved from early death have as good risk as others.

From Table 4 it would appear that mortality from coronary heart disease could be reduced some 18 per cent (9/50th) by special hospital units; but this estimate neglects several considerations. In the first place, coronary patients are generally kept in special units for only four to seven days, almost never for the full four weeks of the "acute period." Therefore it is an over-estimate to suggest that the ordinary mortality rate in the period from two hours to four weeks might be cut by one third with coronary care units as they are now being used. Table 4 also assumes that mortality after discharge from a coronary care unit is the same as in the corresponding period without such units. There are no good data as yet on deaths of patients after discharge, but almost certainly their later mortality rate must be unusually high. This follows from the fact that patients discharged from the unit include some whose condition was so bad that they would have died without the resuscitation facilities of the unit. At best, then, special coronary units cannot greatly improve the one-year prognosis of a heart attack; it is possible that in the long run the mortality improvement may be negligible.

Anticoagulant Therapy

Anticoagulant therapy now seems to be almost routine for the acute period of myocardial infarction and may indeed statistically improve the immediate outlook; but at best the difference is only fractional: a heart attack is extremely dangerous with or without the availability of anticoagulant drugs in the acute period. About long-term anticoagulant therapy there is no agreement that it significantly improves prognosis. Much the same can be said about other "improvements" in the therapeutic arsenal: fibrinolytic drugs, the "polarizing" treatment, drugs to impede arrhythmias. They are interesting and in some cases may be temporarily helpful, but there is no acceptable scientific evidence that they appreciably affect the long-term prognosis of the coronary patient. This is not to decry coronary care units, new drugs and all other modern innovations, but it is necessary to emphasize that the picture of the patient who has clinical coronary heart disease remains dismal. Prevention is essential if this disease is to be brought to an acceptable level of control.

Not long ago pessimists could suggest that it is wishful thinking to talk about preventing coronary heart disease or that the price of preventing coronary heart disease would be

TABLE 5

Deaths from Coronary Heart Disease Among Cohorts of Men Aged 40-59 Followed for 5 Years. The Deaths "Expected" are Calculated from 1962 Death Rates of U.S. White Men Age-Matched by Quinquennia

Cohort	No. of Men	Number of Deaths		
		Observed	Expected	O/E
U.S. railroad men	2576	66	59.7	1.11
East Finland	814	17	17.7	0.96
Dalmatia	669	1	18.0	0.06
Crete and Corfu	1212	4	27.7	0.14

to suffer even more grievously from other diseases. Such negative views, however, cannot be maintained in the face of some recent epidemiological findings. Table 5 provides data that merit careful consideration.

Geographical Variations

The organization, samples, methods, and characteristics of men at entry examination in an international cooperative study[1] concerns individuals aged 40 to 59 who were examined in detail and then followed in regard to the development of heart disease and death. In general, the subjects include substantially *all* men of suitable age in geographically defined areas. An exception is the U.S. sample which was drawn to represent men of the appropriate age employed full time by 19 major railroad companies in the northwest sector of the United States and involved selection towards the absence of disabling disease in that all men were well enough to be employed full time. No such selection affected the men in the other cohorts reported in Table 5.

The contrasts in death rates from coronary heart disease shown in Table 5 are extreme. The U.S. railroad men and the east Finns did not differ in this respect; nor was there any significant difference between the Dalmatians and the Greeks of Crete and Corfu; but the average age-standardized coronary death rate among the U.S. men and the Finns was 9.6 times that among Greeks and Dalmatians. There were similar differences in respect to the incidence of non-fatal coronary heart disease as judged by rigid objective electrocardiographic criteria.

All deaths in this study were reviewed by non-local internists and by a common international panel. Yet the differences in Table 5 are so great as to raise questions about missed diagnoses. Suggestions about missed diagnoses of coronary heart disease are not supported by the all-causes death rate, characterized by the Greeks and Dalmatians, and as illustrated in Table 6.

TABLE 6

Deaths from All Causes Among the Cohorts of Men Represented in Table 5

Cohort	All Deaths Observed	Expected	O/E
U.S. railroad men	125	152.5	0.82
East Finland	64	45.5	1.41
Dalmatia	22	43.1	0.51
Crete and Corfu	21	39.9	0.52

These findings indicate that, somehow, coronary heart disease is promoted in some populatians, including the Finns and the U.S. men, or, conversely, the disease is prevented in other populations such as the Greeks and Dalmatians. Accordingly, it is important to ask, why?

Variable Factors

Three variables frequently proposed as being important in the etiology of coronary heart disease are considered in Table 7.

TABLE 7

Characteristics of the Cohorts of Men Whose Subsequent 5-year Mortality Was Shown in Tables 5 and 6

Cohort	Mean Relative Body Weight	% Heavy Smokers	% Relatively Sedentary
U.S. Railroad men	104	22	52
East Finland	93	31	11
Dalmatia	91	23	8
Crete and Corfu	91	27	17

Smoking Habits and Weight

These men differed little in smoking habits. The east Finns tend to be somewhat heavier smokers as measured by the number of cigarettes a day, but much of the cigarette usage in that cohort involves the Russian type of cigarette which contains much less tobacco than the usual cigarette. In relative body weight there was no significant difference among the three non-U.S. cohorts, but the U.S. men clearly tended to be much more often overweight than the other men. The frequency of excess obesity among the Americans is even more striking when body fat is estimated by measurements of the skinfolds. The average thickness of subcutaneous fat for the Americans was twice that for the other cohorts. The sedentary habits of most of the Americans undoubtedly contribute to the prevalence of obesity.

But the data in Table 7 fail to give any indication as to why the Finns should be so much more prone than the Greeks and Dalmatians to die from coronary heart disease. Being seldom sedentery and rarely obese does not seem to help these Finns who also resemble the Greeks and Dalmatians in living in the quiet countryside, mostly on their own little plots of land, free from the stresses of cities.

Serum Cholesterol and Blood Pressure

The Finns show up badly in two risk factors—serum cholesterol level and prevalence of high blood pressure (Table 8).

TABLE 8

Median Serum Cholesterol Concentration, mg/dl, and Percentage of Men with High Blood Pressure (100 or More in Diastole in Rest) in the Same Cohorts Indicated in Table 7

Cohort	Serum Cholesterol	High Blood Pressure
U.S. railroad men	236	14%
East Finland	265	21%
Dalmatia	186	8%
Crete and Corfu	201	6%

Follow-up studies on men in the United States show that the incidence of coronary heart disease among middle-aged men is increased two to three times by the presence of high blood pressure. On that basis it is interesting to estimate from the data in Table 8 the relative incidence rates that would be expected if the cohorts differed only in regard to blood pressure. With the upper estimate of a three-fold rise in incidence associated with hypertension, and taking the incidence rate in the absence of hypertension as 1.0, the expected over-all rate for the east Finns would be $3 \times 0.21 + 1 \times 0.79 = 1.42$, since 21 per cent of them were hypertensive. For the Greeks and Dalmatians the general average was 7 per cent hypertensive men; so the corresponding calculation is $3 \times 0.07 + 1 \times 0.93 = 1.14$. From these calculations the expectation would be that the incidence rate among the Finns should be $1.42 / 1.14 = 1.25$ times that among the Greeks and Dalmatians. Therefore the difference in the prevalence of hypertension between the cohorts could explain only a very small fraction of the observed difference in coronary mortality.

A similar approach can be used in regard to serum cholesterol. Follow-up studies in the U.S. indicate that the incidence of coronary heart disease among middle-aged men rises to something like the third power of the serum cholesterol concentration.[4] The general average serum cholesterol level of the Greeks and Dalmatians was about 1.95 grams of cholesterol per liter and the third power of $1.95 = 7.41$; for the Finns the average was 2.65 grams of cholesterol per liter and the third power of $2.65 = 18.61$. On this basis alone it could be suggested that the incidence rate of coronary mortality among the Finns might be $18.61 / 7.41 = 2.51$ times that among the Greeks and Dalmatians. So serum cholesterol would seem to explain far more than blood pressure in these comparisons but in itself does not account for the whole difference in the observed mortality.

Comparisons involving the U.S. men are much more complicated because they also involve great differences in physical activity and obesity. From only the characteristics of blood pressure and serum cholesterol the expectation would be that the U.S. railroad men should be intermediate in coronary mortality between the Finns on the one hand and the Greeks and Dalmatians on the other. The data suggest that obesity and lack of exercise contribute to the force of coronary mortality among the Americans. On the other hand, when all causes of mortality are considered, the differences in serum cholesterol and the prevalence of hypertension are parallel to the death rates. In any case, compared with the Americans and the Finns, coronary heart disease is largely prevented among the Greeks and Dalmatians, and it appears that a substantial but far from complete part of the explanation may lie in the serum cholesterol concentration, with blood pressure also playing a role.

In order to focus on prevention, it is necessary to proceed to another question: what are the reasons for the differences in the distributions of serum cholesterol and blood pressure? Currently there is no explanation for the blood pressure differences, no clue as to why the east Finns are three times more prone to hypertension than their counterparts in age, occupation, smoking habits, and body fatness in Greece and Dalmatia. On the other hand, the differences in serum cholesterol are not so mysterious or unexpected.

Influence of Diet

Repeated seven-day dietary surveys, including chemical analyses of the weighed food composites, were carried out on random samples of the cohorts concerned.[5,6,7] Relevant data are summarized in Table 9. Though the average diet of the U.S. railroad men, the east Finns, and the men of Crete provided almost identical percentages of total calories from total fats, the composition of the fats differed. In Finland butterfat is the dominant fat, with very little vegetable fat in the diet. In the U.S., meat fat, especially beef fat, is relatively more important, while in Crete olive oil accounts for some 80 per cent of all fat in the diet. In Dalmatia and Corfu the dietary fat is similarly dominated by olive oil. From these dietary data it would be expected that the serum cholesterol level would be higher in the east Finns than in the Americans who, in turn, would tend to have considerably higher cholesterol values than the men in Dalmatia and Greece.

TABLE 9

Average Percentage of Total Calories Provided by Total Fats and by Saturated (S) and Polyunsaturated (P) Fatty Acids in the Diets of the Men in the Cohorts Considered in Tables 5 et seq. (   )

Cohort	% Calories from:			Median Serum Cholesterol
	Fat	S	P	
East Finland	39.2	22.1	2.9	265
U. S. railroad*	40	18	6	236
Dalmatia	29.5	9.3	6.7	186
Crete	40.3	7.7	2.5	203
Corfu	32.7	5.4	3.5	198

*Chemical composition estimated from tables of food composition.

Comparison between the Finns and the Greeks is particularly interesting because their diets did not, on the average, differ significantly in the percentage of total calories provided by poly-unsaturated fatty acids. On the basis of findings in controlled dietary experiments in the United States, men on diets otherwise comparable but providing 22 versus 6 per cent of calories from saturated fatty acids would be expected to show an average difference of about 43 mg of cholesterol per deciliter of blood serum. The observed average difference was some 20 mg/dl greater, a fact that would be largely if not fully explained by greater intake of exogenous cholesterol in Finland and greater intakes of leguminous seeds, leafy vegetables and fruits in Greece.

Conclusions

This discussion has attempted to make three points. First, in the majority of cases of heart disease specific treatment has great limitations. In the American adult where coronary heart disease accounts for about three fourths of all heart disease deaths and nearly one third of *all* mortality, every consideration leads to the conclusion that prevention of coronary heart disease is essential to make any real impact on the burden of heart disease in the United States. Second, the frequency of coronary heart disease in some populations, notably in the United States and in Finland, is grossly higher than need be, as shown by studies on the incidence of the disease in some other populations. In some populations a very low incidence of coronary heart disease is associated with and productive of remarkably low all-causes mortality rates at ages 40 to 70; it is evident, then, that prevention of coronary heart disease need not lead to compensating increases in other ills. Finally, these differences in coronary heart disease among populations are associated with differences in the level of serum cholesterol and in the frequency of hypertension, risk factors that certainly can be modified by prevention programs. The differences in serum cholesterol level are largely explained by dietary differences. The conclusion is that prevention is not only essential; it is possible.

Acknowledgment

This paper makes use of a small fragment of the data, now being prepared for complete publication, collected in an international cooperative study on the epidemiology of cardiovascular disease for which the author is coordinator. That program, started in 1958, is expected to continue until about 1973. The responsible investigators of the cohorts mentioned here are: Prof. Ratko Buzina, Zagreb (the Dalmation cohort); Prof. Martti J. Karvonen, Helsinki (the east Finnish cohort); Dr. Christ Aravanis, Athens (the Crete and Corfu cohorts); Prof. Henry L. Taylor, Minneapolis (the U.S. railroad cohort). Dr. Henry Blackburn, Minneapolis, has major clinical responsibility in the overall program and Dr. Alessandro Menotti, Rome, has special responsibility for checking interim morbidity and responsibility in Europe.

Hardening of the heart ages people more quickly than hardening of the arteries.

References may be secured from the author or the reprints.

The Evidence for Excess Risk*

in Coronary Disease

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THE NATURAL HISTORY of coronary heart disease as it arises, evolves, and terminates fatally in a general population sample has been investigated prospectively at Framingham, Massachusetts, where 5,127 men and women have been followed biennially since 1949. Since less than 2% have been lost to follow-up some valid conclusions may be drawn.[1-3] One general conclusion indicated by the findings to date is that an approach to this disease is needed which is more comprehensive than that confined to the management of the already symptomatic person. If a substantial reduction in morbidity and mortality is to be achieved it seems clear that concepts of the clinical spectrum of the disease must be broadened to include the asymptomatic phase. We must anticipate the day when a myocardial infarction occurring in a patient under medical surveillance will come to be regarded as a medical failure.

Circumstances of Myocardial Infarction

Sudden Death

Concerning survival, the critical period in a heart attack is the first few minutes. Of all deaths that occurred in initial coronary attacks in the general community more than one half were sudden and unexpected, usually unheralded by any prior symptoms. If sudden death can be included in the syndrome of myocardial infarction, then one in five cases presented with this catastrophe as the first symptom of the disease (Figure 1).

Lack of Recognition

Of all the electrocardiogram-documented infarctions that occur in a community, one in every four is unrecognized. Half of these are silent and the rest so atypical that neither the patient nor his physician even considered the possibility. As a consequence, only about 60% of coronary attacks were hospitalized in Framingham where even suspicion of an attack was cause for a hospitalization. The major reason for non-hospitalization was sudden death and unrecognized infarction. Most myocardial infarctions occur without warning in persons who believe themselves to be in good health. Only about 24% of those sustaining myocardial infarctions had prior symptoms such as angina pectoris.

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†Medical Director, Heart Disease Epidemiology Study, National Institutes of Health, National Heart Institute.

‡Heart Disease Epidemiology Study, National Institutes of Health, National Heart Institute.

Stigmata of Impending Disaster

While most myocardial infarctions occurred unheralded and some never appeared above the clinical horizon, such persons were, however, seldom free of one or more stigmata which could have forecast the impending disaster. Only about 25% were free of one or more predisposing risk factors even 10 years before the attack occurred.

Deciles of Risk*

These hallmarks of unusual susceptibility have been discerned from an examination of the incidence of coronary disease in this general population classified according to antecedent personal characteristics which were believed to be important in the development of this disease. In this way a number of factors have been identified which are associated with increased risk of coronary heart disease. The details of the relationship of these factors to risk of disease have been reported elsewhere.[4-8] Using a number of these identified personal characteristics it is possible to construct, employing discriminant function analysis,[6] a coronary profile for each participant over a thirty-fold range of risks (Table 1). Risk proved to be related to the level of the major blood lipid fractions and to the coexisting blood pressure level. Blood pressure was found to accelerate lipid-induced atherogenesis, whether elevated casually or basally and whether the elevation was systolic or diastolic (Figure 2). The risk was also increased in persons with any evidence of impaired carbohydrate metabolism. Furthermore, the risk of attacks increased alarmingly in proportion to the number

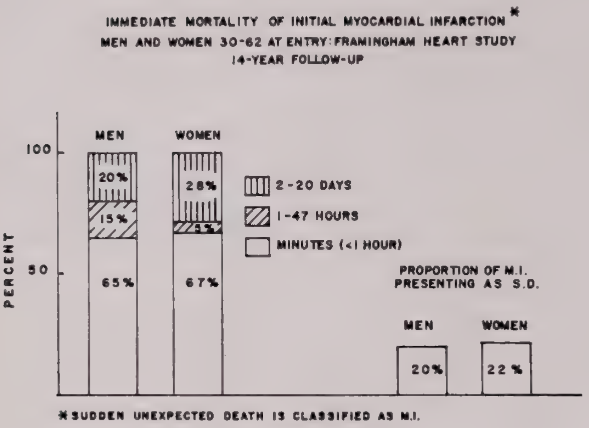

Figure 1

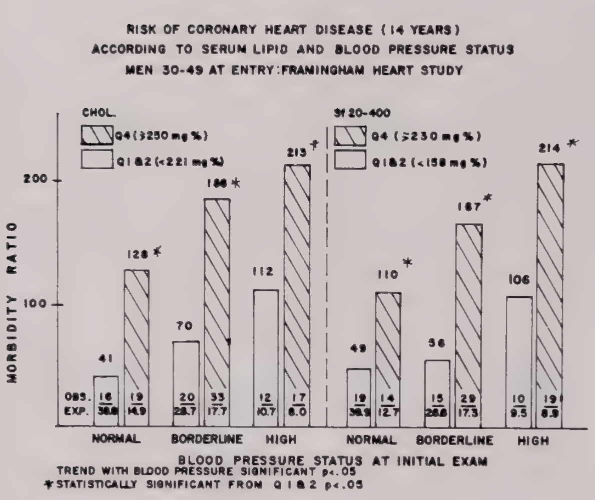

Figure 2

TABLE

12-Year Incidence of Coronary Heart Disease According to Decile of Risk Using Multiple Logistic Function

Decile of Risk*	2187 Men Obs. Cases	Observed 12 Year Incid/1000
10	82	375
9	44	201
8	31	142
7	33	151
6	22	101
5	20	91
4	13	59
3	10	46
2	3	14
1	0	0
Total	258	118

*Deciles of Risk According to Level of all following: Age, SBP, Rel. Wt., Hb., No. Cigs., ECG ABN., Chol.

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*See Test Your Word Score Page 1213.

of these specified atherogenic traits present, particularly the risk of fatal attacks (Figure 3). The appearance of electrocardiographic abnormalities in such highly vulnerable persons appears to predispose to an alarming rate of fatal myocardial infarctions.

The Electrocardiogram

In persons with one or more atherogenic traits, possible evidence of an impaired coronary circulation may be demonstrated even earlier by means of the post-exercise electrocardiogram. The appearance of ischemic electrocardiographic changes provoked by exercise has been convincingly demonstrated by a number of other prospective studies to be associated with a pronounced increase in risk of symptomatic coronary heart disease.[9,10] The post-exercise electrocardiogram may have more utility in detecting asymptomatic persons with a compromised coronary circulation than in clarifying the cause of atypical chest discomfort for which it is principally used today.

The appearance of electrocardiogram abnormalities at rest represents a still more advanced stage of the disease. Such occult coronary heart disease is neither rare nor innocuous. Actual myocardial infarctions as proven by serial electrocardiograms were quite common, occurring with a frequency one third as great as that of symptomatic infarctions. Discounting the immediate mortality, these apparently benign asymptomatic infarctions proved just as deadly as their symptomatically overt counterparts. Within five years one in three of either variety recurred, and in each the case fatality rate was 50% upon recurrence. Even more speculative evidence of coronary myocardial ischemia such as electrocardiographic left ventricular hypertrophy proved surprisingly serious. Such persons ran a risk of symptomatic coronary disease just about as great as persons with angina pectoris, if not equal to those with myocardial infarctions (Figure 4). The mortality in such individuals was also quite comparable to that of persons with symptomatic coronary heart disease. The appearance of this electrocardiographic finding, otherwise unexplained, even in hypertensives should suggest the onset of ischemic coronary myocardial involvement.

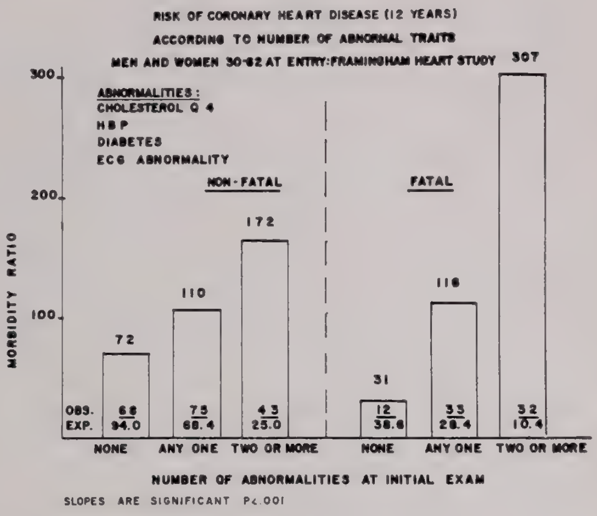
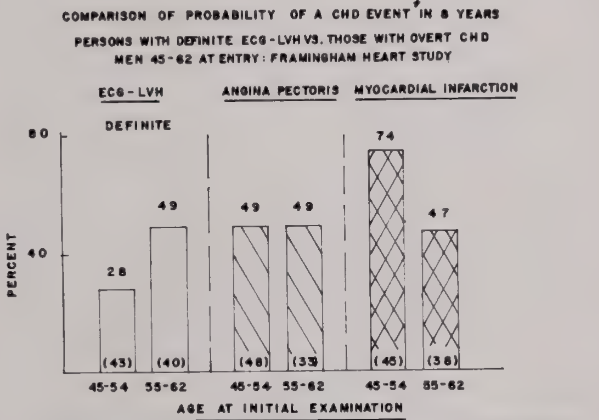


Figure 3



*VARIABLE FOLLOW-UP AFTER APPEARANCE OF ECG LVH AND MANIFESTATIONS OF CHD TAKEN INTO ACCOUNT BY LIFE TABLE ANALYSIS.
ǂM.I. = ANOTHER M.I. OR CHD DEATH
A.P. = M.I., C.I. OR FATAL CHD EVENT
ECG-LVH = ANY CLINICAL MANIFESTATION OF CHD

Figure 4

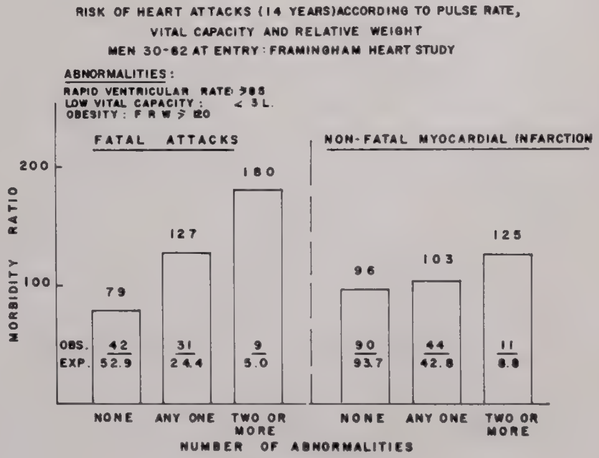


Figure 5

Pre-morbid Management

Recent innovations in the management of acute myocardial infarctions may reduce by as much as one half the deaths occurring in persons who survive long enough to reach the hospital. Selection of patients for admission to coronary care units can be difficult. Unfortunately, the absence of alarming findings on admission is no guarantee against a sudden fatal termination to the illness. Criteria for the selection of such persons requiring management in a coronary care unit may be derived from a study of pre-morbid factors associated with a lethal outcome.

Age

The case fatality rate generally increases with age, but at each age some persons may be identified who are distinctly more vulnerable to a fatal outcome than others. Persons with a prior myocardial infarction and those with electrocardiographic abnormalities such as left ventricular hypertrophy and intraventricular block have a case fatality rate which approaches 50%. Also the case fatality rate increases in proportion to the number of prior atherogenic traits present. Persons with certain possibly sedentary traits such as a low vital capacity, a rapid resting pulse rate and obesity are especially likely to have a fatal attack (Figure 5). It would seem that patients with a combination of atherogenic traits, those with electrocardiographic abnormalities, and those with sedentary attributes are candidates for special coronary care unit management regardless of their clinical condition on admission.

Should the patient survive the initial attack, his troubles are far from over. Most heart attack victims who are free of angina and congestive failure before the attack will continue free of it, and only about 27% will develop angina pectoris they did not have before. Most will be able to return to their usual occupation. The principal hazard lies not in disabling symptoms but in the likelihood of another attack. Depending on age, this relative risk may be five to ten times that of their cohorts free of symptoms of coronary heart disease. As indicated in Figure 4, the absolute risk in men 45 to 62 appears to be in the neighborhood of 50% within eight years. These people also have at least a threefold increased risk of a stroke to add to their burden. Even though asymptomatic, such individuals are in dire need of secondary prevention designed to delay recurrences.

Elimination of Cigarettes

In such susceptible people certain modifications in living habits would seem prudent. The cigarette habit appears to be distinctly pernicious in predisposing to recurrences with fatal outcome. This was true even for persons whose only evidence of ischemic myocardial involvement was asymptomatic electrocardiographic findings (Figure 6). There is much to be gained in giving up the habit since the effects seem to be transient, non-cumulative, and apparently reversible. The risk is related to the number of cigarettes smoked each day, but not to the duration of the habit, so that those who give up the habit seem rapidly to revert to a better risk status.[11,12]

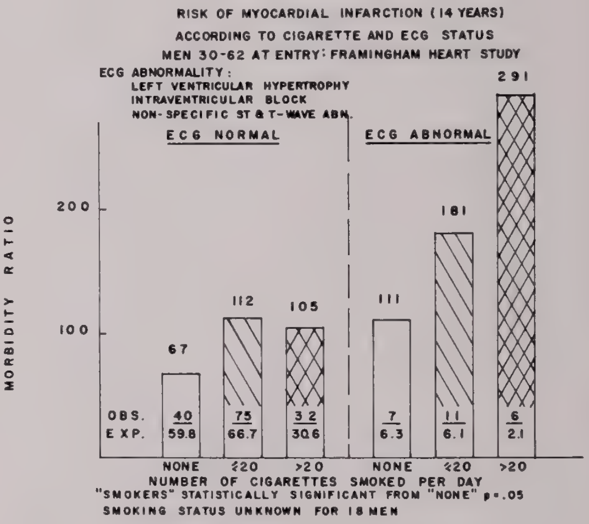


Figure 6

Sloth and Gluttony

Obesity, or the habits of sloth and gluttony which lead to obesity, are apt to bring on angina pectoris and to result in an unusual propensity to sudden death. This was particularly true in those who had predisposing atherogenic traits and, perhaps as a consequence, a compromised coronary circulation (Figure 7).

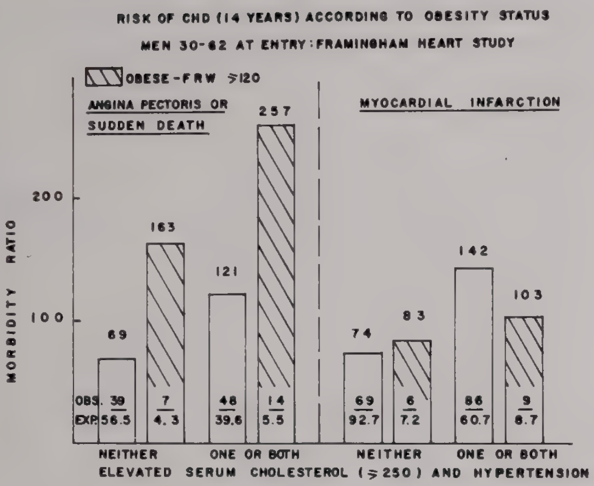


Figure 7

Supervised Exercise

Severe restriction of activity in recovered myocardial infarction victims or in those who are highly vulnerable to it may be unwise, since the sedentary seem to develop an excess of fatal attacks. Promotion of collateral circulation by supervised exercise may afford some protection against a lethal outcome when an occlusion has already occurred.

Conclusions

From an examination of the natural history of coronary heart disease it is apparent that a preventive approach is essential. The measures required are indicated by the factors demonstrated to be associated with an increased risk of attacks and of lethal outcome. While research is urgently needed to demonstrate the efficacy of the preventive measures which seem indicated, the problem is really too serious to permit much temporizing. This is a very common and a very highly lethal disease.

In a ten-year period in Framingham, one in every 10 men and one in every 20 women developed it. The men developed more disease earlier in life and in a more severe form. Evidence has been presented, however, that the disease is not an inevitable consequence of aging or genetic makeup, for at any age in either sex some were identified who were distinctly more vulnerable than others. Such highly susceptible persons can be readily identified by the physician and efforts instituted in an effort to delay attacks.

The general hygienic measures indicated are not easy to implement. Both the physician and the patient would prefer a pill to counteract bad habits. However, the potential for salvage of such vulnerable persons is huge and well worth the effort, whether pharmacologic or hygienic. More effective means for implementing preventive programs which include alteration in diet, maintenance of physical fitness, exercise programs, weight reduction, discontinuing the cigarette habit, and early control of abnormal blood lipids, hypertension and impaired carbohydrate metabolism, are urgently needed. Both the physician and his patient will require considerable assistance in their collaborative effort to achieve these goals.

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Politeness costs nothing and gains everything.—Lady Montagu.

He who neglects the present moment throws away all he has.—Schiller.

Old Hospitals

Hospital of the Holy Spirit, Rome

In medieval Europe, poverty was widespread and social welfare agencies, largely in the hands of the Church, were few. To provide for the sick poor of the city of Rome, Pope Innocent III directed the building of this hospital between the years 1198 and 1201. The Pope brought the newly-founded Order of the Holy Spirit from Paris to operate the hospital under the direction of its founder, Guy de Montpellier. The hospital, in a 13th-century city of hardly 35,000, had a bed capacity of 300 and served 1,000 people per day in what might be called its outpatient department.

The institution became a complete welfare center, operating a maternity home, a nursery, an orphanage, a geriatric nursing home, and a kind of rehabilitation center. It was the first teaching hospital in Rome and has been a center for medical research since the days of Leonardo da Vinci. In the 16th century, its pharmacy played an important part in the distribution of chinchona.

The building shown in this picture was erected in 1478, and is still occupied by patients. Its interior consists of two huge high-ceilinged wards lined with hospital beds. Old frescoes and paintings adorn the walls, and there is a sanctuary and altar between the wards. Under the dome is the hospital board room and a famous library of history of medicine. The hospital is located only a few blocks from the Vatican in the district called Sassia.

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Precautions: Typical penicillin-allergic reactions may occur, especially in hypersensitive patients. Mycotic or bacterial superinfections may occur. Experience in newborn and premature infants is limited and caution should be used in treatment, with frequent organ function evaluations. Safety for use in pregnancy is not established. In gonorrheal therapy, serologic tests for syphilis should be performed initially and monthly for 4 months. Assess renal, hepatic and hematopoietic function intermittently during long-term therapy.

Adverse Reactions: Skin rash, pruritus, urticaria, nausea, vomiting, diarrhea and anaphylactic reactions. Mild transient elevations of SGOT or SGPT have been noted. Black tongue has been noted in some patients receiving the Chewable Tablets.

Usual Dosage: Adults—250 or 500 mg. q. 6 h. (according to infection site and offending organisms). Children—50-100 mg./Kg./day in 3 to 4 divided doses (depending on infection site and offending organisms). Bacterial meningitis—150-200 mg./Kg./day in 6 to 8 divided doses. Children weighing more than 20 Kg. should be given an adult dose when prescribing orally. In parenteral administration, children weighing more than 40 Kg. should be given an adult dose. Beta-hemolytic streptococcal infections should be treated for at least 10 days.

Supplied: Capsules—250 mg. in bottles of 24 and 100. 500 mg. in bottles of 16 and 100. For Oral Suspension—125 mg./5 ml. in 60, 80 and 150 ml. bottles. 250 mg./5 ml. in 80 and 150 ml. bottles. Chewable Tablets—125 mg. in bottles of 40. Injectable—for I.M./I.V. use—vials of 125 mg., 250 mg., 500 mg., and 1 Gm. Pediatric Drops—100 mg./ml. in 20 ml. bottles.

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Warnings: Use with discretion during the second and third trimesters of pregnancy and restrict to patients not cured by topical measures. Flagyl (metronidazole) is secreted in the breast milk of nursing mothers; it is not known whether this can be injurious to the newborn.
Precautions: Mild leukopenia has been reported during Flagyl use; total and differential leukocyte counts are recommended before and after treatment with the drug, especially if a second course is necessary. Avoid alcoholic beverages during Flagyl therapy because abdominal cramps, vomiting and flushing may occur. Discontinue Flagyl promptly if abnormal neurologic signs occur. There is no accepted proof that Flagyl is effective against other organisms and it should not be used in the treatment of other conditions. Exacerbation of moniliasis may occur.
Adverse Reactions: Nausea, headache, anorexia, vomiting, diarrhea, epigastric distress, abdominal cramping, constipation, a metallic, sharp and unpleasant taste, furry or sore tongue, glossitis and stomatitis possibly associated with a sudden overgrowth of *Monilia,* exacerbation of vaginal moniliasis, an occasional reversible moderate leukopenia, dizziness, vertigo, drowsiness, incoordination and ataxia, numbness or paresthesia of an extremity, fleeting joint pains, confusion, irritability, depression, insomnia, mild erythematous eruptions, "weak-

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ness," urticaria, flushing, dryness of the mouth, vagina or vulva, vaginal burning, pruritus, dysuria, cystitis, a sense of pelvic pressure, dyspareunia, fever, polyuria, incontinence, decrease of libido, nasal congestion, proctitis, pyuria and darkened urine have occurred in patients receiving the drug. Patients receiving Flagyl may experience abdominal distress, nausea, vomiting or headache if alcoholic beverages are consumed. The taste of alcoholic beverages may also be modified.

Dosage and Administration: In the Female. One 250-mg. tablet orally three times daily for ten days. Courses may be repeated if required in especially stubborn cases; in such patients an interval of four to six weeks between courses and total and differential leukocyte counts before, during and after treatment are recommended. Vaginal inserts of 500 mg. are available for use, particularly in stubborn cases. *When the vaginal inserts are used,* one 500-mg. insert is placed high in the vaginal vault each day for ten days and the *oral dosage is reduced to two 250-mg. tablets daily during the ten-day course of treatment.* Do not use the vaginal inserts as the *sole* form of therapy. *In the Male.* Prescribe Flagyl only when trichomonads are demonstrated in the urogenital tract, one 250-mg. tablet two times daily for ten days. Flagyl should be taken by both partners over the same ten-day period when it is prescribed for the male in conjunction with the treatment of his female partner.

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Editorials

Prevention of Coronary Disease

ROCHESTER, MINNESOTA, was the scene of a significant symposium conducted in May of 1968 on the subject of the prevention of coronary disease. Doctor Henry Blackburn, the chairman, assembled the papers on the subject presented there and now appearing in this issue of MINNESOTA MEDICINE.

Paul White (The Challenge of Prevention) reviews the history of cardiology in his lifetime which encompasses the modern era. He points out that successful prevention of infectious heart disease, especially rheumatic disease, leaves coronary disease the supreme killer and almost untouched preventatively. Jeremiah Stamler (Reducing Cardiovascular Risk) describes the need for preventive efforts against heart disease in this country. He believes that not more than 10 per cent of hypertensive patients are receiving adequate care. Data from the Coronary Drug Project of which he is chairman show that 50% of males who have had one or more myocardial infarctions are still smoking. The medical profession is overwhelmed by the need for treatment of overt disease and has no time for prophylaxis.

Kannel and McNamara (The Evidence for Excess Risk) in the Framingham Study emphasize the need to investigate asymptomatic disease. One in ten men and one in twenty women in this study developed evidence of coronary disease over a ten-year period. The disease, however, is not the inevitable consequence of aging since at all ages and in both sexes highly susceptible individuals can be identified. They should be intensively treated with regulation of diet, weight, physical activity, smoking, lipid and carbohydrate metabolism, and blood pressure. Dawber (Identification of Excess Cardiovascular Risk) from the same group includes also gout, xanthomatosis, hypothyroidism, and variations of hemoglobin either high or low whose correction may be prophylactic against coronary disease.

Hellerstein (The Effects of Physical Activity) chastises the sedentary, lazy, overweight, hypertensive, smoking, cholesterolemic male for these characteristics. His conditioning program has resulted in improvement that is essentially psychological. He believes a reconditioning program should be prescribed for, among others, "normal" but coronary-prone men.

Nunn et al. (a Lipid Clinic) at the Mayo Clinic have collected 100 hyperlipidemic patients in less than two years. The authors divide them into two lipid populations about half Type II with normal triglycerides and hypercholesterolemia which can be reduced with diet and cholestyramine; and the rest Types II, III, and IV with elevated triglycerides which they treat with diet and clofibrate. Ancel Keys (The Essentiality of Prevention) continues his discussion of the great differences

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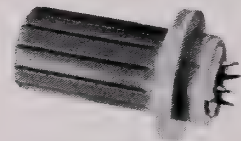

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in populations in incidence of coronary disease. He found a six-fold increase of observed to expected coronary disease in Finns compared to Greeks. This author was privileged to take part in some of these provocative studies which show how greatly coronary disease differs in its incidence throughout the world.

Several papers are concerned primarily with diet (Fetcher: the National Diet-Heart Study; Leren: Plasma Cholesterol Lowering Diet; Dayton and Pearce: Diet High in Unsaturated Fat). Large scale alterations in human diet are feasible and sizeable reductions in plasma cholesterol can be achieved by diet.

Reuben Berman, M.D.
Minneapolis, Minnesota

Physical Activity and the Cardiac Patient

REGULAR PHYSICAL activity in moderation is almost universally considered of psychologic benefit to the participant. Physiologic and metabolic benefits may also be derived, depending on the form and energy-expenditure requirements of the activity. Dr. Oglesby Paul* has pointed out the difficulties in evaluating epidemiologic, pathologic, and physiologic data relating to the role of exercise in coronary atherosclerosis.

Thus far the most objective physiologic response in cardiac patients after a regular exercise program includes a significant reduction in the resting pulse rate, a decrease in the systolic and diastolic blood pressures both at rest and while expending energy, and a significant increase in physical working capacity. The development of collateral coronary artery circulation secondary to increased physical activity has not been studied to the extent that any conclusion can be reached.

Only partial studies of metabolic parameters have been made. Evidence that regular exercise influences cholesterol or triglyceride levels is not conclusive. However, it has been our observation that participants in a program of supervised exercise are better motivated to adhere to a weight-reduction program, and lipid levels subsequently decrease. In a small group of nine patients studied after four to six weeks of exercise, serum lactate levels were lowered.[1]

The psychologic response of cardiac patients to a supervised graduated exercise program is gratifying. Many patients have tailored their physical activities to avoid the annoyance of angina prior to participation. When some degree of physical training has been achieved they become more assertive, hopeful, and occasionally euphoric to a degree that limits must be placed on their physical activity.

The effect of regular exercise on morbidity and mortality has not been satisfactorily discerned but it does seem to be a definite asset in rehabilitating the patient who has angina or who has had a myocardial infarction.

Charles C. Kennedy, M.D.
Rochester, Minnesota

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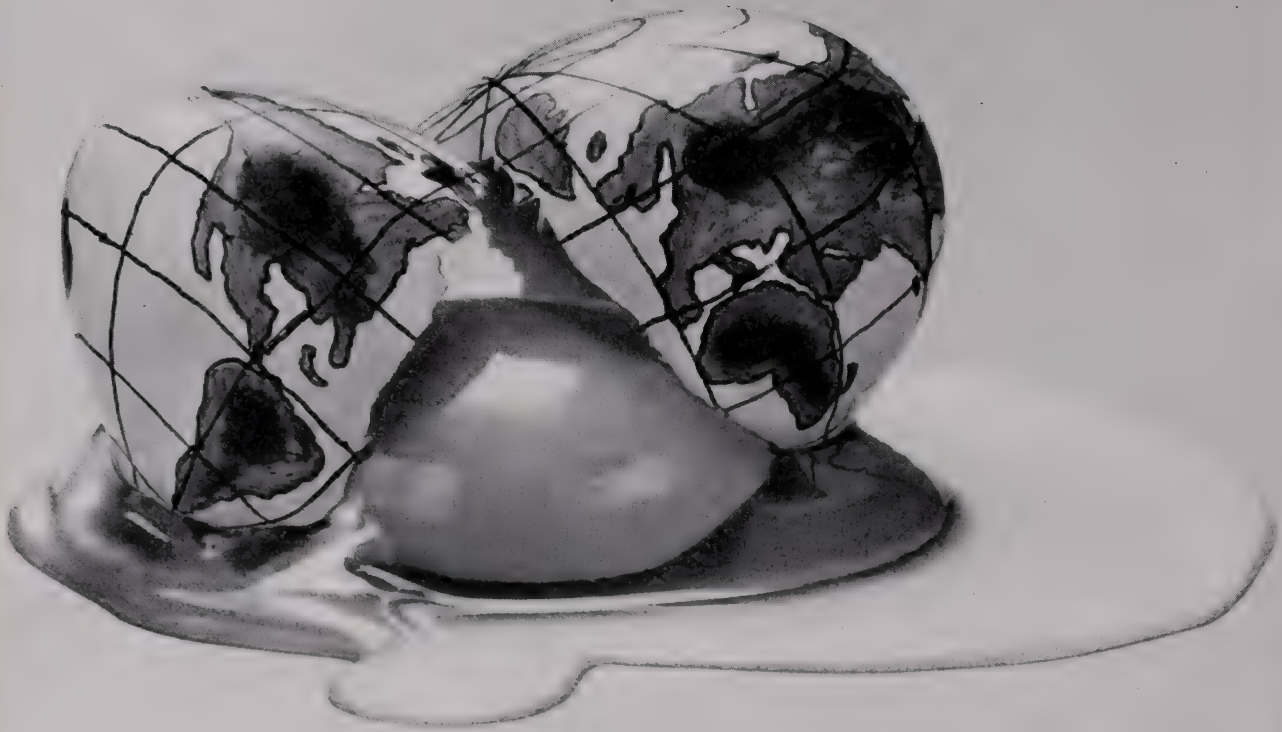
*See page 1327.

Reference

1. Varnauskas, E., Bergman, H., Houk, P., and Björntorp, P.: Hemodynamic Effects of Physical Training in Coronary Patients. Lancet 2:8, 1966.

Men occasionally stumble over the truth, but most of them pick themselves up and hurry off as if nothing had happened.—Winston Churchill



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The Elusive Treatment of Angina

William Heberden introduced the term, angina pectoris, in the mid-eighteenth century,[1] but descriptions of this malady have been noted dating back centuries before his scholarly account of its clinical manifestations. From ancient times to the present, physicians have attempted a variety of therapeutic measures to counter this serious condition; recent years have found medical literature replete with new treatments and modifications of the old. The only specific medication for the relief of angina pectoris to date is the nitrite group of drugs and their exact mode of action continues to be controversial. Nitroglycerin was first introduced scarcely ten years after Heberden's classic description.[2] The intervening years have been both fruitful (considering the large quantity of reseach that has been performed with resultant ancillary benefits) and frustrating (in that a more effective regimen has defied recognition and general acceptance). Psychotherapy, thyroid ablation, anticoagulants, mammary artery ligation, alcohol and physiotherapy are just some of the widely divergent modes of treatment that have met with apparent initial success in recent years. It is safe to assume that none of these measures has thus far stood the test of time as an effective therapy which is relatively free of complications. The same cannot be said at this point for arterial-myocardial diversion (Vineberg) procedures, beta adrenergic blockade or carotid sinus nerve stimulation.

Information continues to increase concerning these three methods. An example of this is found in the paper by Brinkman and Alexander* which appeared in the May issue and was devoted to the clinical experience with propranolol at the Minneapolis Veterans Hospital. The majority of the clinical research with this drug alone and in combination with nitrites has been encouraging since clinical investigation with it was instituted in 1964. Their paper seems to continue this trend. However, as recently as April, 1969, Aranow and Kaplan, in a controlled double-blind study using a combination of propranolol and isosorbide dinitrate, found the following: 30 percent of their experimental patients had fewer anginal episodes while on the drugs, and 44 percent of the control placebo group had fewer anginal episodes.[3] They also noted an apparent superiority of the placebo over the drug combination in exercise performance by a factor of three to four-fold and thereby provoked the question: Are the negative inotropic and chronotropic effects of propranolol, which constitute the physiologic basis for the hoped for reduction in angina, acting as a "double edged-sword" by ultimately increasing myocardial oxygen demand and consumption? Most reports[4,5] are at variance with Aranow and Kaplan and their earlier study using propranolol and isosorbide dinitrate singly and in combination (no statistical difference between treatment and placebo groups),[6] but their paper is most certainly "food for thought."

No clear-cut answer to this elusive problem is apparent, and controversy still rages in discusions of the Vineberg procedure and carotid sinus nerve stimulation as well as beta adrenergic blockade. It has long been recognized that the discomfort so adequately chronicled by Heberden is dependent upon many environmental stimuli and individual variations; one wonders: Could it not be the "subjective nature of the beast" that thwarts our endeavors to efficiently do battle with it?

Marvin S. Segal, M.D.
Minneapolis, Minnesota

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*Brinkman, J. H. and Alexander, C. S.: Propranolol in Angina Pectoris. Minnesota Med 52:725, 1969.

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William Mahoney

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(signed) Suzie McGuire

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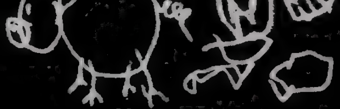
Willie Narner.

Litter is what Bad people do
Pattie Wight

Litter is ugly and ~~dangous~~ ~~danjorus~~ bad.
Tommy Maltby



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Complications of Cardiac Catheterization and Angiography

THE COMPLICATIONS reported by Doctor Hook* are familiar to those working in the field of cardiac catheterization and angiography and emphasize the hazards in these procedures. As the author points out, the benefits of these procedures well justify the risk involved in properly selected cases.

For a cardiac catheterization laboratory to function successfully in a community general hospital several requirements must be met. The laboratory should be under the direction of a cardiologist with experience in performing the various procedures and in evaluating and selecting the patients to be studied. The cooperation of the radiologist is important to obtain the maximum benefit from the procedures. A cardiovascular surgeon should be available in the hospital to aid in the management of the occasional complication and also to participate in the function of the laboratory. Adequate technical help often means the difference between a successfully and a poorly functioning laboratory.

As in other areas of medicine, the successful function of a cardiac catheterization laboratory depends on close cooperation between all of the individuals involved. With properly trained individuals and support from the hospital board, there is no reason why these studies cannot be performed in community hospitals.

David A. Berman, M.D.
Minneapolis, Minnesota

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*Hook, W. F.: Complications in a Small Heart Laboratory. Minnesota Med, 1967.

Test Your Word Score

Deciles—*any one of ten groups* (page 1198).

Electrophoretic—*characterized by the movement of particles in an electric field toward anode or cathode* (page 1219).

Domiciliary—*in residence* (page 1237).

Myristic—*designating a crystalline fatty acid found in nutmeg butter, spermacetti, coconut oil, bile, lanolin, etc.* (page 1250).

Lauric—*designating a white crystalline fatty acid found in the berries of the laurel* (page 1261).

Calorie—*an amount of food having an energy-producing value of one large calorie* (page 1263).

Rubric—*an established rule or custom* (page 1269).

Bivariant—*capable of twofold variation* (page 1272).

Atherogenic—*having the capacity to initiate, increase or accelerate* (page 1273).

Anorexigenic—*tending to depress appetite* (page 1279).

Honorable Mention

The June issue* carried the announcement of the MINNESOTA MEDICINE Medical Writing Honor Award winners for 1969.

Now the Board of Editors proudly lists in this issue the authors who received honorable mention for their presentations:

Name	*Manuscript*	*Issue*
Milton Alter, M.D. *Minneapolis*	*Examination of the Comatose Patient*	*September*
Milton Alter, M.D. and *William Kennedy, M.D.* *Minneapolis*	*The Marinesco-Sjogren Syndrome—*	*July*
Robert B. Breitenbucher, M.D. *Minneapolis*	*Acute and Subacute Fibrinopenic Syndromes*	*February*
Henry Buchwald, M.D., *Gerald B. Lee, M.D.,* *Kurt Amplatz, M.D.,* *Richard B. Moore, M.D.,* *Ivan D. Frantz, Jr., M.D., and* *Richard L. Varco, M.D.* *Minneapolis*	*Severe Atherosclerotic Cardiovascular Disease in a 14-Year-Old Homozygous Familial Hypercholesterolemic*	*April*
E. B. Cohen, M.D. *Minneapolis*	*Early Diabetes Mellitus*	*October*
Charles M. Evarts, M.D. *Cleveland, Ohio*	*The Fat Embolism Syndrome*	*August*
Alfred Gutgemann, M.D. *Bonn, Germany*	*Surgery of Gastric Carcinoma*	*November*
William J. Kane, M.D. *Minneapolis*	*Lower Limb Amputations in Peripheral Vascular Disease*	*February*
C. Kaufer, M.D. *Bonn, Germany*	*Etiology of Consciousness Disturbances in Surgery*	*November*
Arthur C. Klassen, M.D. *Minneapolis*	*Vertebral-Basilar Insufficiency*	*September*
Jose C. Pacheco, M.D., and *William J. Martin, M.D.* *Rochester*	*Endotoxic Shock in Obstetrics and Gynecology*	*April*
Theodore A. Peterson, M.D.; *Frank E. Johnson, M.D. and* *Joseph C. Kiser, M.D.* *Minneapolis*	*Esophageal Resection—* *Gastroesophageal Anastomosis*	*October*
Edson H. Rafferty, B.S., *Harold Kletschka, M.D.* *Martin Wynyard, M.D.* *John T. Larkin* *Louise V. Smith* *Betty Cheathem* *Houston, Texas and* *Syracuse, New York*	*Artificial Heart—Parts I and II*	*January and February*
Richard L. Reece, M.D. *Minneapolis*	*An Analysis of 4000 Chemistry Graphs—*	*March*
William J. Riley, M.D. *Minneapolis*	*Internal Carotid Insufficiency*	*September*
Marshall D. Schechter, M.D. *Oklahoma City, Oklahoma*	*A Psychological Field Theory of Adolescence*	*December*
William E. Segar, M.D. and *Ward W. Moore, M.D.* *Rochester*	*Hyponatremia*	*May*
Leslie W. Tasche, M.D. *Sheboygan, Wisconsin*	*1700 Vaginal Hysterectomies*	*December*

The Editors again wish to express their thanks and applause to all of the above distinguished authors.

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*See pages 937 and 939.

The Editor's Soliloquy

The "In-Thing" To Do

"YOU MUST BE a professor, correcting all those papers," was the introductory remark of a young college sophomore who stopped by to pass the time of day. We were in the Vistadome of the Great Northern "Empire Builder" as I was on my way home from a medical search-out.

I had been musing on the baffling paradoxes that belie the adjective *sapiens* in man's proud arrogation of the term *Homo sapiens*: So far as I am aware, no other animal persists so consistently and conspicuously in behaving in his own worst interest: smoking, over-eating, excessive drinking, and inadequate exercise. Weren't cigarettes long ago termed "coffin nails" —long before any remote linkage with lung cancer was suspected? Yet now, with all their notoriety as carcinogenic agents, has not their consumption increased in alarming proportion to the population? The reason I suspect is their glamorization.

"No," I was merely doing a bit of editing of manuscripts for our medical journal: exposing the hazards to the cardiovascular system to which millions of people deliberately, sometimes defiantly, sometimes cavalierly, expose themselves by their excesses.

I was startled but pleased by the student's interruption of my reverie, subsequently even more pleasantly surprised when the young man informed me that at his school, Malta High School, Montana, most of the students, both boys and girls, had renounced the habit of smoking. In a total of 350 registrants, he further announced, there were only five or six hold-outs. That sounded incredible! And if he knew the secret of its accomplishment the American Cancer Society should surely hear about it!

The student body had voted to discuss the question: to smoke or not to smoke; a few simple scientific facts were brought out; medical research was cited; the sensuous and psychic pleasures of cigarette smoking were assessed and objectively weighed against the health hazards. A few influential students expressed their mature opposition to the pernicious habit; emotion and sentiment were disavowed; families' wishes and crusaders' exhortations were dismissed as irrelevant! No rewards would be forthcoming; no pledges or promises solicited! Emotional outbursts were repudiated as immature and in poor taste.

The student body registered the majority opinion that the "in-thing" to do, if offered a cigarette, was to say simply: "No, thank you"—with no ifs, ands or buts; no explanations, no apologies, no holier-than-thou implications.

"Have a cigarette?"

"No, thank you."

Carl O. Rice, M.D.

Old Doc Hess Says: Unasked advice is rarely welcome.

Minnesota Medicine Survey

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2. The advertisements. None, 25%, 50%, 75%, 100%.

3. Indicate the percentage of time in which you read the following sections:

____ Scientific; ____ Editorials; ____ Letters to the Editor; ____ Editor's Soliloquy; ____ Quotes at the bottom of article; ____ Full page fillers; ____ Viewing Box; ____ CPC's; ____ Curbstone Consultations; ____ Fracture Conferences; ____ Tumor Conferences; ____ Grand Rounds; ____ Advances; ____ Reviews; ____ Physician's Workshop; ____ Special Articles; ____ Meetings & Announcements; ____ Lab Letters; ____ Physician's Diary; ____ Dermatology; ____ Abstracts; ____ Test Your Word Score; ____ Book Reviews; ____ History of Medicine; ____ In Memoriam; ____ Minnesota Medicine at a Glance.

4. Which section do you read the least ____________________.

5. Your Specialty ____________________? Resident ____________________?

Intern ____________________? Medical Student ____________________?

6. Suggestions: ____________________

____

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Identification of Excess Cardiovascular Risk*

A Practical Approach

THOMAS R. DAWBER, M.D.†
Boston, Massachusetts

FOLLOWING THE RESULTS of research which suggests merit in new diagnostic, therapeutic or preventive procedures in medicine, there is a period of uncertainty during which a clarification of the practical usefulness of the procedures takes place. Some procedures can be adopted directly; others require considerable modification, and some turn out to be impracticable.

The demonstration, primarily through epidemiologic investigations, that certain constitutional and environmental characteristics are related to the development of coronary heart disease has brought about exploration into methods of favorably changing these characteristics. Moreover, studies have been undertaken to determine whether changing them is effective in reducing the risk of coronary heart disease development. In most instances the results are still inconclusive because of insufficient numbers of subjects observed over inadequate time.

Critics challenge the role which various risk factors play in the development of the disease. Others accept their role but doubt that effective means of changing them are available or acceptable to medical consumers. Others question whether "proof" of any benefit from changing the "risk factors" has been established. Most admit that the relative importance of various risk factors so far identified needs elaboration, and that unidentified risk characteristics, such as those related to hypercoagulability, must be sought. Though the methods for changing risk characteristics are far from perfect, and the evidence of benefit from change still has to be obtained, reasonable physicians act in accordance with the maxim of Dr. Samuel Johnson that "Nothing will ever be attempted if all possible objections must first be overcome." They wish to identify persons at unusual risk and to attempt the indicated changes, anticipating a beneficial result.

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*Presented at the Minnesota Symposium on Prevention in Cardiology, May 2-3, 1968 in Rochester, Minnesota.

†Associate Professor of Medicine, Boston University Medical Center.

Usefulness of Preventive Measures

The acceptability by physicians of the usefulness of a procedure is not always based on factual evidence. For example, physicians continue to accept, and in fact strongly advocate, surgery for certain types of malignant tumors in spite of weighty evidence that this form of treatment is not really effective. The surgical removal of tumors *seems* a rational treatment, and once a form of therapy becomes common practice it is usually accepted uncritically for a long time.

At present it appears reasonable to advocate changes in risk factors, even in the absence of complete evidence of the value of such procedures. Meanwhile, research into the benefit of changing risk factors, the degree of change required, the best methods of making the changes, the ages of the population at risk when changes would be most effective, etc. should be top priority in medical research.

Physicians who accept the usefulness of preventive measures in coronary heart disease must make certain decisions regarding which individuals are at sufficient risk to warrant an attempt being made to mitigate that risk.

Examples of questions to be answered are the following:

1. What populations should be selected for risk factor modification?
2. Which tests are both useful and practicable for the M.D. to use in his office?
3. At what point does the risk become sufficiently great to warrant medical interference.

The answers to these questions are relative rather than absolute and require individual judgment. General guidelines have been developed by the American Heart Association and published in its statement on Risk Factors and Coronary Heart Disease (1968).

Selection of the Population at Risk

It is first necessary to consider groups in which the risk of subsequent coronary heart disease is sufficiently high to warrant attempted modification. The general population at highest risk of coronary heart disease development can be divided into three major categories. Some comments about these groups are in order.

Overt Disease

Recognized

Recent studies have suggested that persons with known myocardial infarctions can decrease their recurrence rate by judicious prophylactic procedures. Since those who already present evidence of disease are at the top of the list of risk for future serious heart attacks, it seems wise to bring them under medical supervision. These include persons with known angina pectoris, coronary insufficiency and myocardial infarction who require investigation to find defects which may be partially responsible and which can be changed (e.g., blood pressure, lipid abnormality).

Unrecognized

About 25% of all cases of myocardial infarction are unrecognized. These can be detected only by routine electrocardiographic tracings recorded as part of an examination of all men over age 40 and all women over age 50. This procedure should be made a part of community screening programs and of detection in the physician's office. In community programs it is possible to screen large numbers of persons in a short time. The diagnosis of angina pectoris in doubtful cases can be confirmed by the performance of an exercise test, such as a step test. This is also practicable for use in the physician's office. Asymptomatic myocardial ischemia (asymptomatic electrocardiogic changes brought on by exercise) can also be detected in a fraction of the apparently well population. This approach, however, appears to have a doubtful place in screening other than to assist in the differential diagnosis of chest pain of undetermined nature.

Recognizable Diseases Associated with Coronary Heart Disease

Xanthomatosis

This familial disorder is almost always associated with hypercholesterolemia. In addition, coronary heart disease is quite common, often occurring at a very early age. The presence of xanthomatosis, whether tendinous, tuberous, or eruptive, calls for detailed lipid studies, i.e., serum cholesterol, triglycerides and electrophoretic* patterns.

In addition to xanthomata, xanthelasma also may be evidence of an abnormality of cholesterol metabolism. Approximately 50% of persons with xanthelasma will have elevated serum cholesterol levels. Xanthomatosis itself is very rare in the general population; xanthelasmata are much more common.

Diabetes Mellitus

The increased risk of coronary heart disease in subjects with diabetes mellitus makes it worthwhile to try to detect this disease, even in a "mild" state. As a routine procedure, determination of blood sugar three hours after a meal of moderate carbohydrate intake is recommended. When it is not possible to impose a fixed time interval following a meal, casual blood sugars with notations regarding the time since eating, and the composition of the meal, will suffice. In this situation, if elevated blood sugar levels are detected, retesting is necessary with a three-hour postprandial blood sugar determination. Occasionally, a complete glucose tolerance test may be indicated. When the physician makes a diagnosis of diabetes, even of minimal severity, he should make a detailed evaluation of the serum lipids.

The continued high rate of coronary heart disease in diabetics who are under "good" medical management for their carbohydrate metabolic defect suggests that current diabetic therapy is insufficient and that careful attention should also be paid to correcting the lipid abnormality.

Gout

Since an elevated blood uric acid level predisposes to both gout and coronary heart disease, the serum uric acid should be estimated in men with a history of gout or other joint disorder.

Hypothyroidism

Though hypothyroidism with associated hypercholesterolemia may predispose to coronary heart disease, data from the Framingham Study suggest that neither hyper- nor hypothyroidism is sufficiently common in the general population to warrant a screening protein-bound iodine determination unless there is reason to suspect thyroid metabolic abnormality. Anyone with symptoms suggesting hypothyroidism should have careful evaluation of his thyroid state.

No Recognizable Disease but Measurable Risk

In the remaining "well" population with neither overt coronary heart disease nor evidence of any other definable disease, it is desirable to identify those persons at sufficiently high risk to warrant intervention. Distinction between those with "disease" and those without disease as discussed above is relatively sharp. No such sharp distinction, however, can be made between those with risk factors and those without. Rather, the physician must decide at what point on a continuous curve the risk is high enough to warrant the effort required to lower the risk.

In its statement on Risk Factors and Coronary Disease, the American Heart Association recommends that "individuals with a twofold or more increase in risk be referred to physicians for prophylactic management." Individuals with any of the following findings fit into this level of risk.

Serum Lipids

There is little doubt that certain abnormalities of lipid metabolism are related to the development of coronary heart disease. This includes certain recognizable familial diseases. Other acquired diseases which present evidence of lipid abnormalities, e.g., biliary cirrhosis and nephrosis, have not been related to coronary heart disease development, but this is probably because the diminished life span of the intrinsic disease precludes a study of this relationship. Lipid tests include:

Inspection of blood serum (or plasma) for turbidity. If the serum is clear, the presumption is that the triglyceride levels are not elevated. But absence of turbidity is not proof that such elevation does not exist. Cloudiness of serum, however, may be the result of alimentary hyperlipemia, and serum must be inspected after at least 12 hours of fasting. If still turbid, a presumption of elevated triglycerides is made.

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*See Test Your Word Score Page 1213.

In any case, determination of total serum cholesterol is required. If the cholesterol level is not elevated (see Risk Factor Statement of American Heart Association) and the fasting serum is clear, no further study of blood lipids is required. If the serum is cloudy, determination of the triglycerides is warranted. Electrophoretic lipid patterns are rarely needed, if cholesterol and triglyceride determinations are available.

Determination of total serum cholesterol is sufficient both for screening purposes and for routine check-up examinations in the absence of possible lipid metabolic disease (known coronary heart disease, family history of coronary heart disease, evidence of gout, etc.).

The impression has been created that carbohydrate-induced hyperlipidemia is the only important lipidemia related to atherosclerotic disease. Too much emphasis has been placed on this entity in view of its relatively slight contribution to atherosclerotic disease.

If diabetes is detected by determination of carbohydrate metabolic defects, there is little reason to measure other lipids than total serum cholesterol, among the general population. The evidence still points to the level of serum cholesterol as the most important lipid measurement to consider in the screening and prediction of coronary heart disease.

Blood Pressure

The importance of elevated blood pressure in the production of coronary heart disease is generally accepted. Experts debate the relative merits of the measurement of casual versus basal blood pressure, the importance of fixed versus labile pressure, and of systolic pressure versus diastolic. Important to the practicing physician is the predictive value of the casual pressure which can be taken in his office. Clearly blood pressure is a variable characteristic and in general is more variable the higher the level.

Studies in Framingham have clearly established that classification of subjects on the basis of the initial casual blood pressure measurement agrees well with a similar classification using the mean of a series of such measurements over time. However, the physician must determine the blood pressure in the same way in all patients if he is to attach importance to the casual measurement. For screening purposes, the evidence indicates that the initial casual blood pressure suffices. In order to decide what to do about a particular blood pressure level, the physician may wish to determine the mean value of a series of blood pressures. Nurses' and technicians' readings are generally lower than physicians'.

Hemoglobin or Hematocrit

In view of the increased rate of coronary heart disease and stroke at both low and high levels of hemoglobin and hematocrit, the determination of either of these measurements appears desirable in screening procedures in the community and in office practice. Simple devices for hematocrit determination are readily available and practicable.

Vital Capacity

A relationship between vital capacity and risk of subsequent coronary heart disease has been demonstrated in the Framingham data. The better the vital capacity, the lower the risk. A number of associations can be found between vital capacity and other measurements, such as height, which in turn are also related to coronary heart disease risk. Vital capacity is probably a resultant of a number of factors including physical activity and body build. The recording of a timed vital capacity provides a permanent record for future comparison, when a decrease in vital capacity may signal impending congestive failure or when changes in the pattern may signal emphysema or obstructive bronchopulmonary disease.

Physical Strength

At the present time there is insufficient evidence that degrees of physical activity are important in contributing to the morbidity rate of coronary heart disease. However, people who are more physically active are more likely to survive heart attacks once they have occurred. Some measure of "physical activity" is desirable for classifying subjects, and in calling attention to lack of "physical fitness." A proper assessment might involve a number of muscle-testing procedures but is not practicable. Limited measurements, such as hand-grip strength, are of some value and can be included in a battery of tests with little expenditure of time.

Weight and Fat Measurement

Weight measurement is routine in most physicians' offices. The absolute degree of over- or underweight or the percentage by which the individual is over- or underweight must then be determined.

But how much of the excess weight is undesirable fat? Elaborate techniques must usually be employed for the latter. Simple weight-for-height, compared to standard tables, may be satisfactory. Additional measurements of fat using calipers may also be used.

Present evidence suggests that it is primarily those with considerable excess weight who have an increased risk of coronary heart disease development. Data from Framingham indicate that a degree of overweight which is 30% or more above that expected can definitely be labelled a risk factor.

Summary

Many epidemiologic studies have demonstrated that certain host and environmental factors are clearly related to a high risk of development of subsequent coronary heart disease. These characteristics may be grouped into three categories:

(1) Those persons already presenting evidence of existing coronary heart disease, much of which may be subclinical.

The inclusion of an electrocardiographic examination in the routine physical examination of all adults will disclose almost all subclinical coronary heart disease. Persons presenting with chest or related pain of undetermined etiology may require exercise electrocardiograms.

(2) Those persons with certain other diseases which clearly predispose to early coronary heart disease.

Included are xanthomatosis and familial hypercholesterolemia, diabetes mellitus, gout, and hypothyroidism. Persons with these diseases should be considered candidates for early development of coronary heart disease. They should have careful evaluation of blood lipids, blood pressure and other risk factors mentioned below.

(3) Apparently well people in whom certain findings are present which increase the risk of coronary heart disease development.

In this well population the following factors should be looked for and can be measured by the practicing physician in his office or in a community detection program.

Conclusions

In almost all instances the measurement of total serum cholesterol is all that is required.

Casual blood pressure as measured by the practicing physician is adequate for detection purposes. The physician faced with a decision as to whether treatment is indicated and the type of treatment to be selected may require more elaborate investigation.

Weight for the individual's height group compared to standard tables will allow the patient to be classified in terms of relative weight. Persons who are 30 per cent or more above weight are at a definitely increased risk of coronary heart disease development.

Measurements of physical fitness are relatively crude. Vital capacity and measurement of hand-grip strength will give some suggestion of physical fitness.

Elevation of these measurements increases the risk of thrombotic disorders. Inclusion of these measurements is therefore indicated in any screening program or office evaluation.

Man

There are three classes of men in the United States—the intellectual, the handsome, and the majority.—Construction Digest.

The power imprisoned in the atom is not greater than the power imprisoned in the human soul.—Forbes Epigrams

Nobel Prize Winners in Medicine and Physiology

Christiaan Eijkman 1929

For his Discovery of the Antineuritic Vitamin

"An accident set me on the right road.

"In the chicken-run of the laboratory in Batavia there suddenly broke out a disease which was in many ways strikingly similar to human beri-beri, and hence invited penetrating study.

"As may already be guessed from the symptoms (unsteady gait, muscular weakness, collapse, progressive paralysis, cyanosis, or blueness of comb and skin, stupor, subnormal temperature, and death) and the course of the disease, and as microscopic study confirmed, it was a question of a polyneuritis.

"As regards etiology . . . search for infection, using materials from sick animals or those that had died of the disease, gave no clear result, while all the hens, including those kept separate as controls, were affected. No specific microbe was found, nor any higher organized parasite.

"Then all at once our opportunity for further researches disappeared, as the disease came suddenly to a stop. The sick hens got better and no new cases appeared. Fortunately suspicion was then directed toward food.

"The laboratory was still temporary, and very meagerly housed in the military hospital, although it was administered under the civil authority. The laboratory attendant, his motive economy, had now, as I first learned later, obtained cooking rice from the hospital kitchen to use as chicken-feed. Then, the cook having been transferred, his successor objected to military rice going to civilian hens. So it happened that the hens were fed with cooking rice only from the 10th of June to the 20th of November. But the epizootic began on the 10th of July and ended in the last days of November.

"Deliberate feeding experimentation was then undertaken. This definitely showed that the polyneuritis had its origin in the cooking-rice feed. The hens were thereby subjected to the disease after 3-4 weeks, while the controls fed with unhulled rice remained healthy.

"This rice still has the inner hull and contains the germ, wholly or in part. As could then be concluded from many different experiments, the effective antineuritic principle occurs particularly in these parts of rice—and of cereal grains generally."*

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*Theodore L. Sourkes: Nobel Prize Winners in Medicine and Physiology, 1966.

Petrarch to the Pope in 1352

"I am much alarmed, gentle Father, to hear of your sickness (typhus fever), and this news sent a frosty shiver over my limbs. I know that your bedside is beleagured by doctors, and naturally this fills me with fear. As Pliny said, 'In order to make a name for themselves through some novelty, they traffic with our lives. With them, not as with other trades, it is sufficient to be called a physician to be believed to the last word, and yet a physician's lie harbors more danger than any other. They learn their art at our expense, and even our death brings them experience: the physician alone has the right to kill with impunity.'

"Oh, Most Gentle Father, look upon their band as an army of enemies. Remember the warning epitaph which that unfortunate man had inscribed on his tombstone: 'I died of too many physicians.' "*

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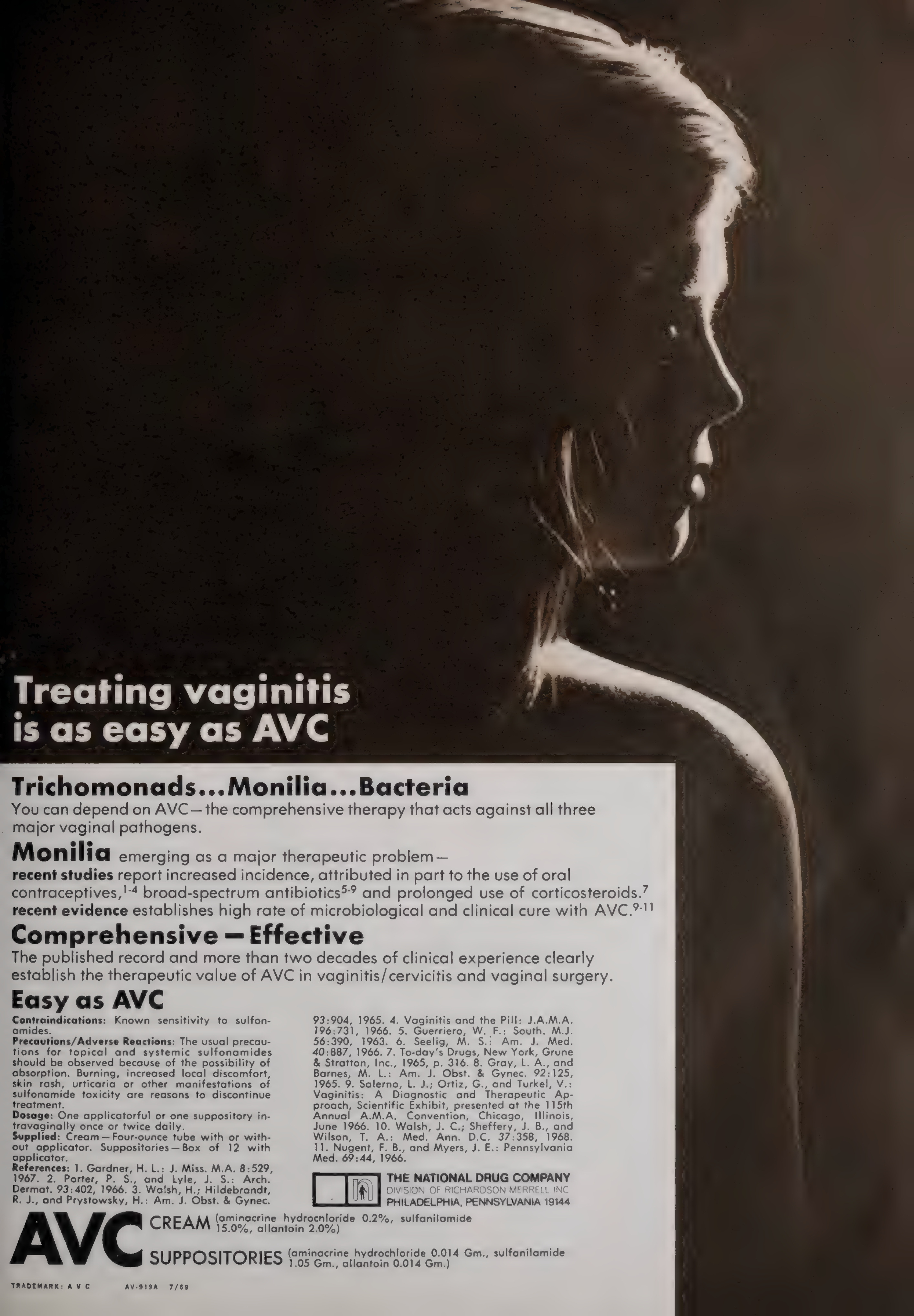
*Saul, F. William, M.D.: Pink Pills for Pale People, 1949.



Treating vaginitis is as easy as AVC

Trichomonads...Monilia...Bacteria

You can depend on AVC—the comprehensive therapy that acts against all three major vaginal pathogens.

Monilia emerging as a major therapeutic problem—

recent studies report increased incidence, attributed in part to the use of oral contraceptives,[1-4] broad-spectrum antibiotics[5-9] and prolonged use of corticosteroids.[7]

recent evidence establishes high rate of microbiological and clinical cure with AVC.[9-11]

Comprehensive—Effective

The published record and more than two decades of clinical experience clearly establish the therapeutic value of AVC in vaginitis/cervicitis and vaginal surgery.

Easy as AVC

Contraindications: Known sensitivity to sulfonamides.

Precautions/Adverse Reactions: The usual precautions for topical and systemic sulfonamides should be observed because of the possibility of absorption. Burning, increased local discomfort, skin rash, urticaria or other manifestations of sulfonamide toxicity are reasons to discontinue treatment.

Dosage: One applicatorful or one suppository intravaginally once or twice daily.

Supplied: Cream—Four-ounce tube with or without applicator. Suppositories—Box of 12 with applicator.

References: 1. Gardner, H. L.: J. Miss. M.A. 8:529, 1967. 2. Porter, P. S., and Lyle, J. S.: Arch. Dermat. 93:402, 1966. 3. Walsh, H.; Hildebrandt, R. J., and Prystowsky, H.: Am. J. Obst. & Gynec. 93:904, 1965. 4. Vaginitis and the Pill: J.A.M.A. 196:731, 1966. 5. Guerriero, W. F.: South. M.J. 56:390, 1963. 6. Seelig, M. S.: Am. J. Med. 40:887, 1966. 7. To-day's Drugs, New York, Grune & Stratton, Inc., 1965, p. 316. 8. Gray, L. A., and Barnes, M. L.: Am. J. Obst. & Gynec. 92:125, 1965. 9. Salerno, L. J.; Ortiz, G., and Turkel, V.: Vaginitis: A Diagnostic and Therapeutic Approach, Scientific Exhibit, presented at the 115th Annual A.M.A. Convention, Chicago, Illinois, June 1966. 10. Walsh, J. C.; Sheffery, J. B., and Wilson, T. A.: Med. Ann. D.C. 37:358, 1968. 11. Nugent, F. B., and Myers, J. E.: Pennsylvania Med. 69:44, 1966.

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SUPPOSITORIES (aminacrine hydrochloride 0.014 Gm., sulfanilamide 1.05 Gm., allantoin 0.014 Gm.)

TRADEMARK: A V C AV-919A 7/69

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Trypsin: 100,000 N.F. Units, Chymotrypsin: 8,000 N.F. Units.; equivalent in tryptic activity to 40 mg. of N.F. trypsin

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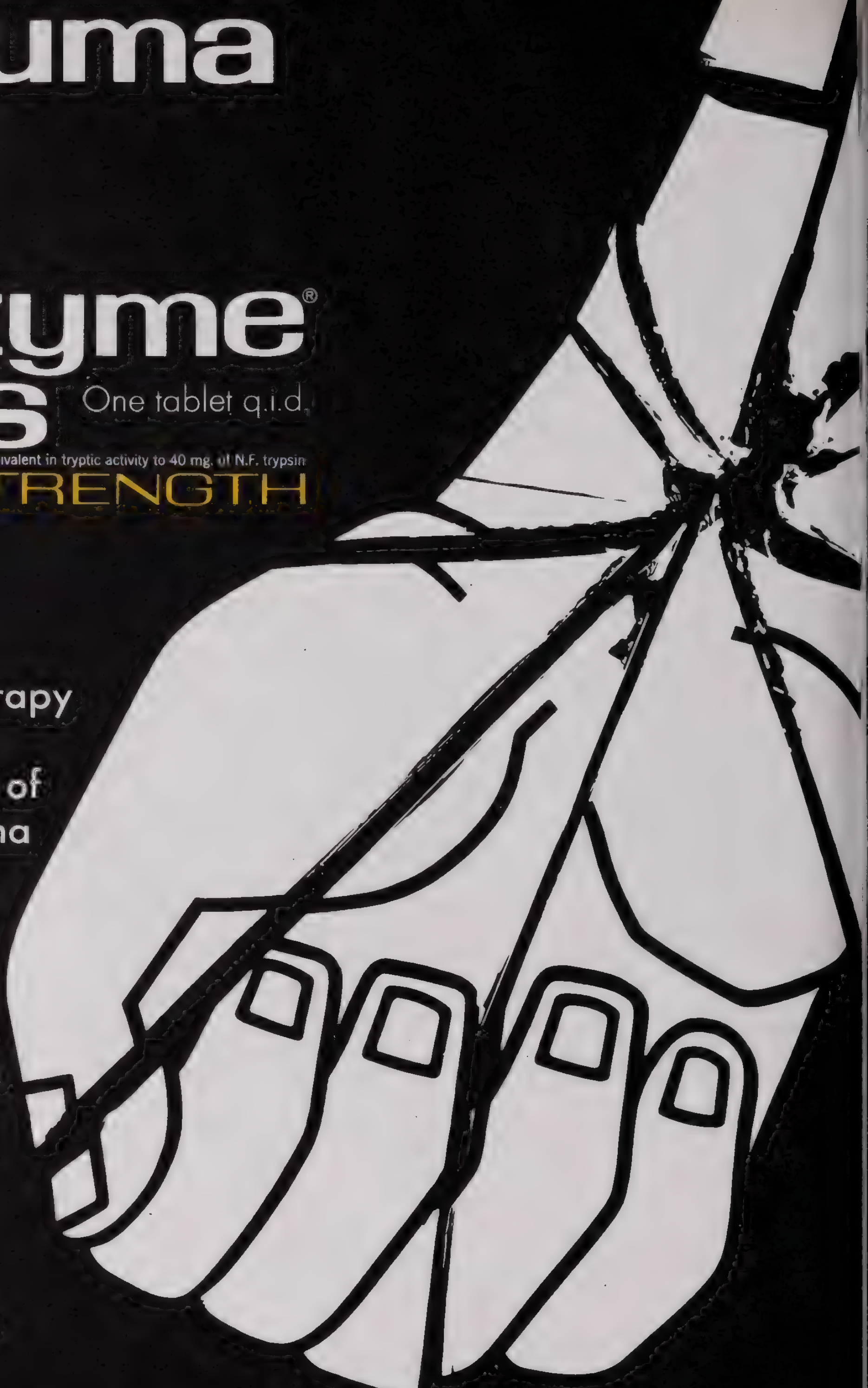

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1 tablet q.i.d. provides recommended therapeutic dose at lower cost.

A FULL DAY'S DOSAGE

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☐ Accidental Trauma
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Other conventional measures of treatment should be used as indicated. In infection, appropriate anti-infective therapy should be given.
Contraindications: ORENZYME BITABS should not be given to patients with a known sensitivity to trypsin or chymotrypsin.
Precautions: It should be used with caution in patients with abnormality of the blood clotting mechanism such as hemophilia, or with severe hepatic or renal disease. Safe use in pregnancy has not been established.

Adverse Reactions: Adverse reactions with ORENZYME have been reported infrequently. Reports include allergic manifestations (rash, urticaria, itching), gastrointestinal upset and increased speed of dissolution of animal-origin surgical sutures. There have been isolated reports of anaphylactic shock, albuminuria and hematuria. Increased tendency to bleed has also been reported but, in controlled studies, it has been seen with equal incidence in placebo-treated groups. (See Precautions.) It is recommended that if side effects occur medication be discontinued.
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Serum Lipid Fractions and Risk of Coronary Heart Disease*

The Framingham Study

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An impressive array of evidence has accumulated which links the total blood cholesterol with the development of atherosclerosis and coronary heart disease. This has stimulated much research concerning the role of lipids in atherogenesis and, as a result, virtually every blood lipid fraction has been incriminated. Nevertheless, the lipid component most basic to the atherosclerotic process remains in doubt. There are, in particular, little prospective data on which to judge. Those lipid elements incriminated in atherogenesis include cholesterol, triglyceride, phospholipid and nonesterified fatty acids. In addition, the lipoproteins and proteins which transport the lipids about in the blood have also been blamed. These include the cholesterol-rich beta-lipoproteins of the Sf 0-20 class, the triglyceride-rich pre-beta-lipoprotein of the Sf 20-400 class, the alpha-liproprotein rich in phospholipids, and the albumin fraction which carries the fatty acids about. Whether one or several of these are fundamentally involved in the pathogenetic process of atherosclerosis is not clear.

The Study Procedure

At Framingham 5,127 men and women have been followed over 14 years in a prospective study of the risk of developing manifest coronary heart disease. These individuals were classified on the basis of their cholesterol and phospholipid levels and on their serum beta and pre-beta-lipoprotein concentration early in the course of the study. Laboratory methods employed, diagnostic criteria, sampling procedures, response rates, and completeness of follow-up have been reported elsewhere.[1-10] Beta-lipoprotein fractions were measured at the Donner Laboratories under the supervision of Dr. John Gofman.

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*Presented at the Minnesota Symposium on Prevention in Cardiology, May 2-3, 1968 in Rochester, Minnesota.

†Medical Director, Heart Disease Epidemiology Study, National Institutes of Health, National Heart Institute.

‡Heart Disease Epidemiology Study, National Institutes of Health, National Heart Institute.

Results

The Lipid Characteristics

On follow-up of this population sample classified according to lipid characteristics, it became apparent that the risk of every manifestation of coronary disease was distinctly and impressively related to the level of each lipid and liproprotein vehicle studied. Thus, risk was related to the concentration of cholesterol, Sf 0-20 beta-lipoprotein, Sf 20-400 prebeta-lipoprotein (and to the level of phospholipid). Comparing the first with the fourth quartile, each lipid presents a gradient of risk which does not immediately suggest one particular lipid as most basic to the problem of atherosclerosis.

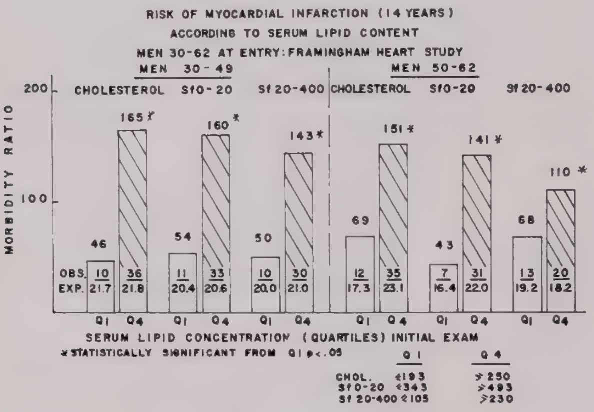

Figure 1

Figure 1 shows, furthermore, that each lipid was a better predictor of disease when measured prior to age 50 than when measured later in life. As illustrated for the beta-lipoprotein fractions in Figure 2, within the range of lipids encountered in this population, neither a safe nor a critical level of any of these lipids could be identified. Rather, the risk was proportional to the level of the lipid from the lowest to the highest values recorded in the population. The lipid levels in this population, however, are uniformly high. The antecedent lipid level was found to predict disease long in advance of its occurrence as well as in the short term.

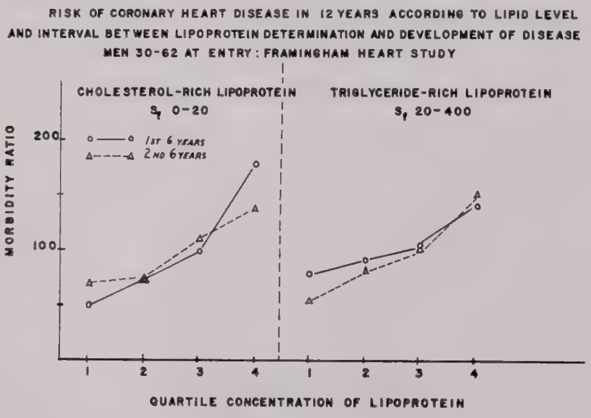

Figure 2

The Lipoprotein

No prospective data are available at Framingham for whole serum triglyceride. However, fasting whole triglyceride levels in cases compared with matched controls were examined, revealing that they are indeed higher in persons with established coronary disease, in agreement with the findings of others.[11,12] Prospective data for the Sf 20-400 pre-beta-lipoprotein, reflecting endogenous triglyceride, revealed that this lipoprotein fraction is related to risk of coronary disease in both younger and

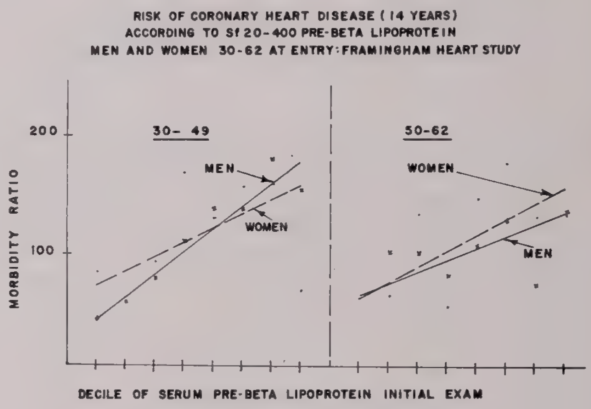

Figure 3-a

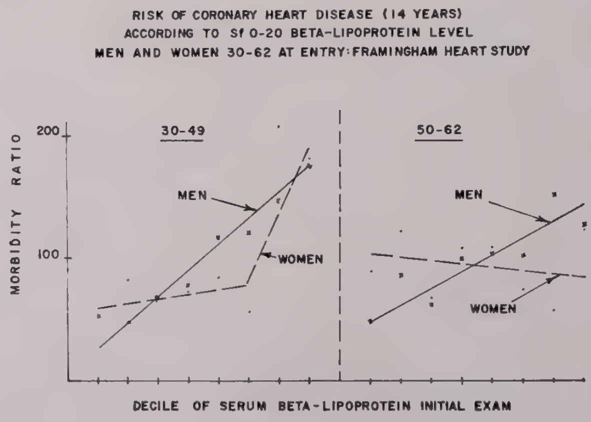

Figure 3-b

older women. The beta-lipoprotein of the Sf 0-20 class, on the other hand, is related to disease outcome in women below 50, but not above this age. In men, both of these fractions are related to risk of disease at all ages, and again it is stronger before 50 than after (Figures 1 and 3-a, and b).

Cholesterol and Endogenous Triglyceride

An examination of the risk of disease according to the level of both cholesterol and endogenous triglyceride in the serum, (as reflected by the Sf 20-400 lipoprotein fraction) reveals that each contributes to the risk. It seems clear that the risk associated with one rises in proportion to the level of the other. Whether the cholesterol was high or low, the risk rose with the level of the triglyceride. The converse was equally true. Those with both values high seemed to be worse off than those with either high alone (Figure 4). This would suggest an independent effect of each. Furthermore, as indicated in Figure 5 the risk rises, particularly in young men, in proportion to the number of lipid "abnormalities" if the value at the upper quartile of the distribution of each lipid is chosen as "high." This would also suggest that each lipid contributes to risk of disease. However, it is difficult to say whether this is actually so. As the Table shows, these lipids are highly correlated so that the level of any particular lipid also rises with the number of lipid abnormalities present. Con-

TABLE

MEAN LIPID AND LIPROPROTEIN CONTENT ACCORDING TO NUMBER OF LIPID "ABNORMALITIES"
Men 30-62 at entry—Framingham Heart Study

Men 30-49 No. of Lipid Abnormalities	No.	Mean Serum Lipid Content S_f20-400 Lipoprotein	S_f0-20 Lipoprotein	Serum Cholesterol	Serum Phospholipid
None	746	126.7	363.6	197.2	143.8
One	309	189.8	434.9	222.5	178.7
Two	211	259.5	479.1	248.0	200.0
Three	136	339.7	501.2	285.4	236.5
Four	65	345.9	567.2	293.0	249.9
Men 50-62					
None	277	121.8	363.8	197.2	149.6
One	151	188.5	447.0	223.4	178.5
Two	94	221.7	480.4	253.5	205.7
Three	80	274.6	523.4	280.9	225.4
Four	25	357.8	586.6	291.8	258.2

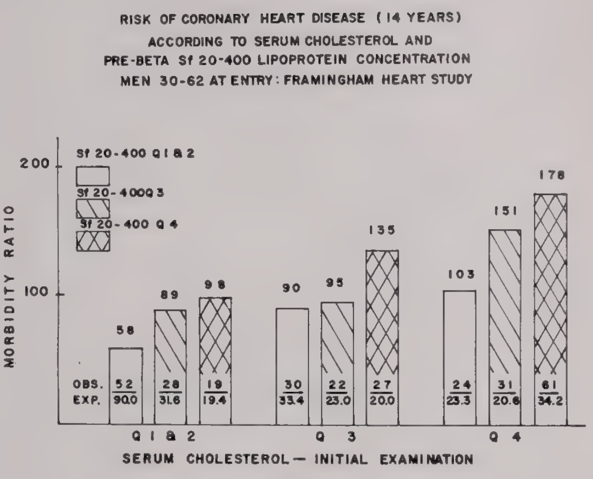

Figure 4

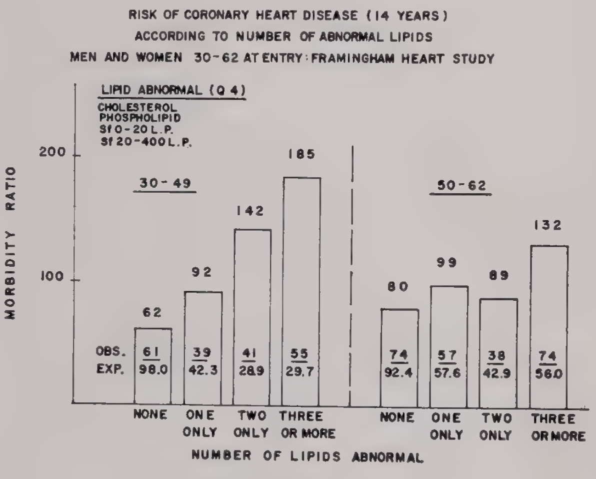

Figure 5

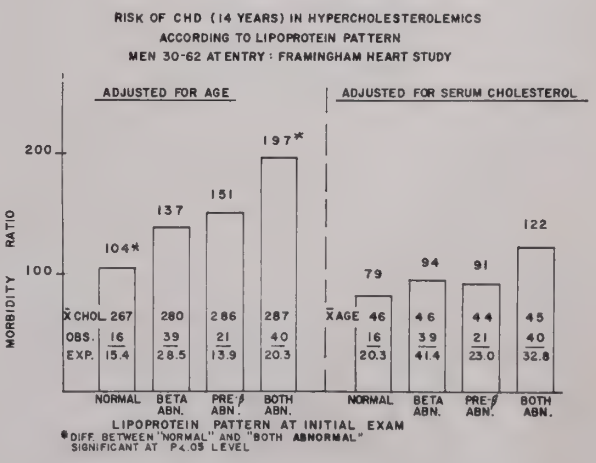

Figure 6

sequently, it is difficult to assess the net effect of each lipid fraction as a contributor to risk. Discriminate function analysis will be employed in an attempt to determine the net and joint effect of these lipids.

The Sf 20-400 pre-beta-lipoprotein level reflects endogenous triglyceride which becomes elevated in endogenous or carbohydrate-inducible hyperlipemia and in persons with diabetes.[13-15] This fraction also carries some cholesterol and, as a consequence, marked elevations may raise the total serum cholesterol concentration. An elevated cholesterol occurring in association with a high 20-400 pre-beta-lipoprotein concentration may, as a result, reflect a metabolic alteration different from that which occurs in association with beta-lipoprotein elevation of the Sf 0-20 class.

Figure 6 shows a further classification of persons with elevated cholesterol levels according to their associated lipoprotein pattern, whether predominantly beta or pre-beta or both. This suggests some differences in risk depending on the associated lipoprotein pattern. Those with both lipoproteins elevated appeared to have the highest risk, but they also had the highest average cholesterol. Whatever the pattern, it is clear that hypercholesterolemia is not innocuous. The risk generally tends to be proportional to the cholesterol level irrespective of the associated lipoprotein pattern. However, adjustment for cholesterol variations between the groups does not entirely eliminate the differences, although they are no longer statistically significant. Since adjustment for the differences in cholesterol content failed to obliterate the effect of the associated liproprotein pattern completely, it cannot be concluded on this evidence alone that risk is entirely or uniquely related to the level of cholesterol.

Obesity-Diabetes-Gout

Lipoprotein abnormality is associated with the occurrence of obesity; persons who gained weight tended to have their cholesterol level rise, particularly if they were not already obese. To an even greater extent their Sf 20-400 or pre-beta-lipoprotein level likewise tended to rise with weight gain. Diabetics also tended to have abnormal lipids, as did persons who developed gout. These conditions have been noted to be associated with an increased risk of coronary heart disease. The two major lipoprotein fractions, the beta cholesterol-rich and the pre-beta triglyceride-rich fractions, seem to contribute to risk even in persons who are not overtly diabetic, obese or gouty (Figure 7). This strongly suggests that the lipid is the culprit and not the associated metabolic abnormalities, although it is difficult to completely exclude latent metabolic alterations.

Once an attack occurred, the case fatality rate also appeared higher in those with preexisting elevated cholesterol levels. Evidently elevated cholesterol levels predisposed not only to the occurrence of attacks, but to failure to survive an attack once it occurred.

Hypertension

In animal experiments lipid-induced atherosclerosis is accelerated when hypertension is

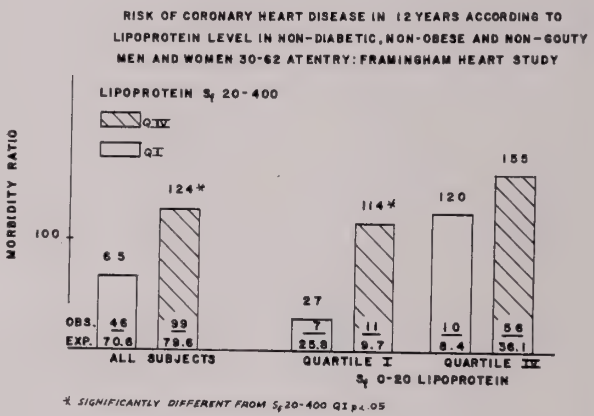

Figure 7

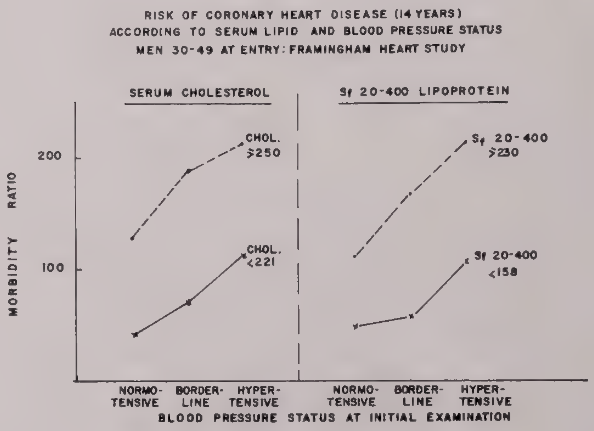

Figure 8

also induced.[16-21] Epidemiologic data appear entirely consistent with this experimental evidence. Elevated lipid or lipoprotein is more atherogenic, as evidenced by the development of clinical coronary heart disease, when accompanied by hypertension. A further increment in risk is noted in "hyperlipemic" persons as the blood pressure goes from normotensive to hypertensive levels. A high lipid level is much less ominous in normotensive individuals, being associated with a risk only modestly above the standard risk. Conversely, at any level of lipid the risk is proportional to the blood pressure level (Figure 8).

Comments

The total cholesterol appears to predict coronary heart disease as well as any other lipid or lipoprotein, but knowledge of the lipoprotein pattern may be important for other reasons. Hypercholesterolemia may be sensitive to dietary saturated fats or cholesterol. This type is apt to be associated with elevated beta-lipoprotein; but it may also be carbohydrate-sensitive and associated with pre-beta-lipoprotein.[13-15] Hypercholesterolemia may likewise be associated with high levels of both lipoproteins. If the fourth quartile concentrations used in this analysis have validity in a metabolic sense, then about half of hypercholesterolemics are at least partially carbohydrate-inducible or carbohydrate-sensitive. This may explain why the standard saturated-fat and cholesterol-restricted therapeutic diet is only moderately successful in reducing the serum cholesterol level.

Isolated cholesterol abnormality of the carbohydrate-inducible type is relatively uncommon, and the saturated fat and cholesterol-sensitive type associated with beta-lipoprotein is still the most common variety. High serum cholesterol concentrations can also occur in the absence of any dietary indiscretion, and these will sometimes not respond to any type of dietary manipulation. This is particularly true of the familial hypercholesterolemia in which there is a beta-lipoprotein abnormality without any trace of an abnormality in the pre-beta-lipoprotein.

Measures designed to alter the cholesterol:phospholipid ratio would appear futile. When hypercholesterolemic individuals are examined according to their cholesterol:phospholipid ratio there is no suggestion that high phospholipid levels actually protect persons with high cholesterol values (Figure 9). The effect of phospholipid, if any, would appear additive.

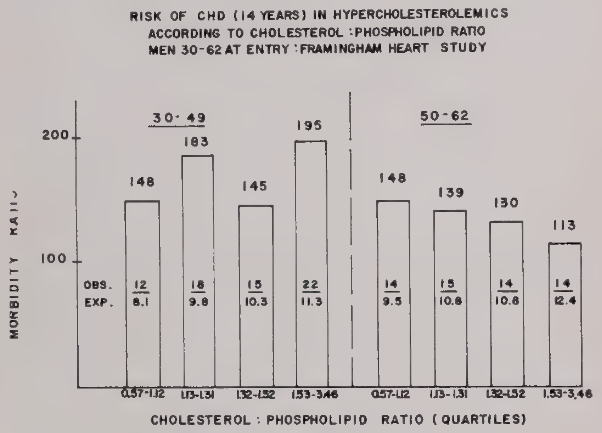

Figure 9

By usually accepted standards hypercholesterolemia does not appear to be an essential feature of atherosclerotic disease in Western civilization. Almost everyone appears to have high enough serum lipid concentrations to produce atherosclerosis. With the generally high lipid levels seen in Framingham, the risk is simply proportional to the level of a variety of lipids. Coronary heart disease is best characterized as a multifactorial disease involving an interplay of a variety of noxious factors. The more of these present, the more ominous is the contribution of the lipid to the disease outcome. When these factors are not present, lipid makes a much more modest contribution to risk.

Some persons question whether the association of lipid with atherosclerotic disease is more than a coincidence or perhaps an indicator of a more basic problem. There is also controversy as to whether hyperlipidemia is primarily an inborn metabolic error or an acquired trait. By any criterion, however, the evidence linking lipids to atherosclerosis is substantial. One most important piece of evidence, however, is still lacking. It has not been conclusively demonstrated in man whether correction of a particular lipid abnormality will result in a better prognosis or a resolution of atherosclerotic lesions; but evidence is beginning to accumulate.[22-24] Until this last link in the chain of evidence is provided, uncertainty regarding the role of lipids in atherosclerosis will continue.

Conclusions

While it appears likely that the blood lipid content, augmented by elevated blood pressure, is related to the rate of general deposition of atheromatous material, it seems clear that local factors exert a marked influence on the site of arterial deposition. These factors include the dynamics of flow, the caliber of the vessels, the metabolism of the vessel wall, and factors which promote thrombus formation and fibrin deposition. Whether the problem is primarily a genetic one involving inherited inability to cope with dietary saturated fat, cholesterol or carbohydrate, or is the result of prolonged overloading of a normal metabolic mechanism is still unknown. The answer to this question is fundamental to an understanding of the pathogenesis of atherosclerosis. At the present time the lipoprotein pattern in hypercholesterolemia would appear more important in determining the reason for cholesterol elevation and in selecting the best therapy than for estimating risk. No clear separation of potential cases from their disease-resistant cohorts appears to be achieved by further classifying hypercholesterolemic individuals according to their lipoprotein pattern.

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Overweight

Diet: Something to take the starch out of you

A secret is what you tell someone else not to tell because you can't keep it—Herbert Prochnow

Plasma Cholesterol Lowering Diet*

The Effect in Male Survivors of Myocardial Infarction

PAUL LEREN, M.D.†
Oslo, Norway

THE PURPOSE OF THE present study was to evaluate what effect a reduction of the plasma cholesterol concentration by means of diet would have on morbidity and mortality from coronary heart disease (coronary heart disease relapses) in male survivors of myocardial infarction.

A pilot study which preceded the present trial demonstrated that a sizeable plasma cholesterol reduction could be achieved by the planned experimental diet, and valuable experiences were gained.

The present material consisted of 412 males aged 30-64, and discharged from medical departments in Oslo during the years 1956-58, with a first diagnosis of myocardial infarction. They were allocated at random to the experimental diet group and to the control group, one to two years after their infarction.

At the start of the trial it was decided that the trial should last for exactly five years.

The comparability of the groups was thoroughly studied, and it was found that they were strictly comparable except for blood pressure. However, blood pressure was slightly higher in the diet group.

Only one coronary heart disease relapse was counted in each patient, the order of priority being: myocardial reinfarction, new cases of angina pectoris, and sudden death. Criteria for the diagnosis of reinfarction were established, and the decision was left to a diagnostic board which did not know to which group the patient belonged.

A close follow-up study was undertaken, including clinical examination with diet and weight control, serum cholesterol determination and electrocardiography, and a review of hospital records.

The Diet

The cholesterol-lowering diet was low in animal fats and in dietary cholesterol, and rich in vegetable oil.

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*Presented at the Minnesota Symposium on Prevention in Cardiology, May 2-3, 1968 in Rochester, Minnesota.

†Assistant Professor, Oslo Kommune, Ulleval Hospital, Department VIII, Oslo, Norway.

The complete report is available in a booklet, published by Universitetsforlaget, Oslo, 1966. It was also published as Acta Medica Scandinavica Supplement 466, 1966.

In an analysis of the experimental diet as consumed by 17 selected dieters, the mean daily intake was 92 g protein, 104 g fat, 269 g carbohydrates, and 264 mg cholesterol. Daily intake of calories was 2,387.

Fat calories covered 39 per cent of total calories. The sources of fat were soy bean oil (72 per cent), fish fat (11.6 per cent), animal fat (8.8 per cent), cereal fat (5.0 per cent), and fat from other sources (2.6 per cent). Of the mean dietary fat, 21.6 per cent was saturated, 25.7 monounsaturated, and 52.7 polyunsaturated.

Results

The mean reduction of serum cholesterol in these 17 dieters was 31 per cent.

Essential details of instruction and training were given. The adherence to the diet was controlled by close personal contact assisted by a full-time, experienced dietitian working in the homes of the patients. The degree of adherence could be quantified by means of a detailed questionnaire used six times during the observation period.

Of the dieters, 62.2 per cent were judged to be "excellent" adherents, 22.1 per cent "good," 10.3 per cent "fair," and 3.9 per cent "bad."

Judging by personal contact with the controls and by a questionnaire at the end of the trial, and also by the serum cholesterol level, which remained nearly unchanged from the beginning to the end, it can be assumed that the type of food in the control group remained largely unchanged.

At the start of the trial the mean serum cholesterol value was exactly the same in the two groups (296 mg per 100 ml). From the first control examination, three months later and throughout, a significant difference in the serum cholesterol level persisted (Figure 1). The mean cholesterol reduction in the diet group was 17.6 per cent against 3.7 per cent in the control group. Of the dieters, 123 obtained a serum cholesterol reduction of $\geqq 15$ per cent, against 27 of the controls.

Myocardial Reinfarction

In the diet group 43 myocardial reinfarctions occurred in 34 patients, 10 of them fatal. In the control group, 64 myocardial reinfarctions occurred in 54 patients, 23 of them fatal.

The difference between the groups is statistically significant (reinfarction patients: $x^2 = 5.22$, $p = .022$, fatal reinfarctions: $x^2 = 4.74$, $p = .029$). But the difference did not become statistically significant until the third year of the trial.

Angina Pectoris

Of 75 dieters and 79 controls who did not have angina pectoris at the start of the trial, 10 dieters and 29 controls acquired angina during the observation period. Of these, two of the dieters and nine of the controls also had reinfarctions and have been counted as such. After excluding these patients, the difference between the groups is still statistically significant ($x^2 = 4.61$, $p = .031$).

Sudden Death

The incidence of sudden death was the same in the two groups, 27 in each. This result was not surprising. Sudden death is considered in most instances to be caused by ischemia, provoking electrical instability followed by ventricular fibrillation or heart stand-still. It is reasonable, therefore, that sudden death in survivors of a myocardial infarction, presumably with rather advanced atherosclerosis, is less related to the degree of atherosclerosis than to other factors, such as the localization of the lesions to more vulnerable areas.

Total CHD Relapses

The total number of coronary heart disease relapses was 80 in the diet group and 120 in the control group. These relapses occurred in 64 dieters and in 90 controls. The difference is statistically significant ($x^2 = 6.48$, $p = .011$), and the difference became significant during the second year of the trial.

As the diagnosis of angina pectoris can be difficult and possibly influenced by personal

TABLE

	Diet	Control
No. of men at entry	206	206
Fatal relapse (fatal reinfarct + sudden death)	37	50
Non-fatal reinfarct	24	31
Major CHD relapse	61 (P = .05)	81
All cardiovascular deaths	38 (P = .09)	52

bias, only major coronary heart disease relapses are counted in the Table. The total cardiovascular mortality as calculated by "life-table" methods is presented in Figure 2.

Age Factor

Subdividing the material into age groups, those below 60 years and those of 60 years and older, revealed that the difference in the coronary heart disease relapse rate was statistically significant only in the patients below the age of 60. So too was the relapse combination, myocardial infarction and acquired angina pectoris. The incidence of sudden death was the same in the two groups, independent of age.

In the diet group as well as in the control group, the serum cholesterol level was higher in the patients with coronary heart disease relapses than in those without. Subdivision of the material revealed that this difference in the serum cholesterol level was also limited to those under 60 years of age who had myocardial reinfarctions and acquired angina pectoris. At the age of 60 and above, there was no difference in the serum cholesterol level between those with and without coronary heart disease relapses.

No association was found between the serum cholesterol level and the incidence of sudden death in either of the two age groups.

The coronary heart disease relapses were also related to other possible coronary risk factors.

Risk Factors

Body weight had no definite influence on the serum cholesterol level or on the coronary heart disease relapse rate, except that the

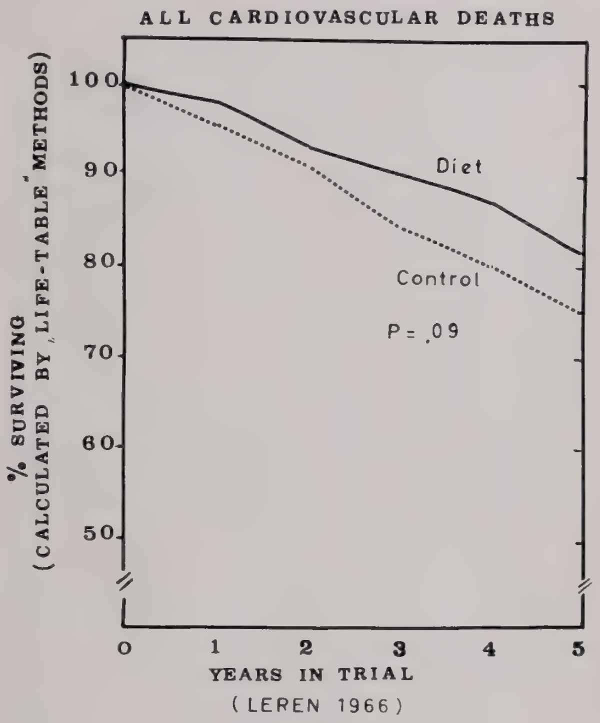
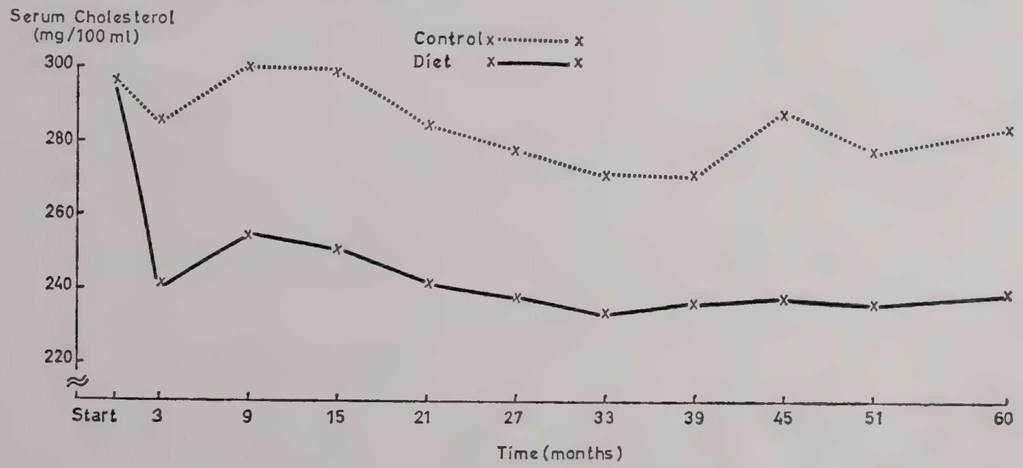


Figure 2



	N (at start)	Start value (mg/100 ml)	Mean reduction (mg)	Mean reduction (per cent)
Control:	206	296	11	3.7
Diet:	206	296	52	17.6

Fig. 1—Serum cholesterol levels in the diet and the control group during the observation time.

cholesterol level tended to be reduced in those underweight.

Blood pressure had no definite influence on the coronary heart disease relapse rate in the diet group. In the control group there was a strong trend, though statistically not significant, toward a higher coronary heart disease relapse rate in the hypertensives. This was especially true when serum cholesterol at the start was ≧ 275 mg per 100 ml. The difference in coronary heart disease relapses between these normotensive and hypertensive controls very narrowly escapes the five per cent level of significance ($x^2 = 3.22$, $p = .073$).

Smoking habits did not influence the serum cholesterol level or the coronary heart disease relapse rate in the control group. In the smoking dieters there was a suggestion, although statistically nonsignificant, toward a higher coronary heart disease relapse rate ($x^2 = 2.78$, $p = .096$).

The presence of angina pectoris at the start of the trial increased the coronary heart disease relapse rate in both groups, especially the incidence of sudden death, which in both groups together was significantly higher in those with angina than in those without ($x^2 = 7.30$, $p = .007$).

The effect of cholesterol reduction was most pronounced in those without angina pectoris at the start of the trial. The difference in the coronary heart disease relapse rate between these dieters and controls was highly signifi-

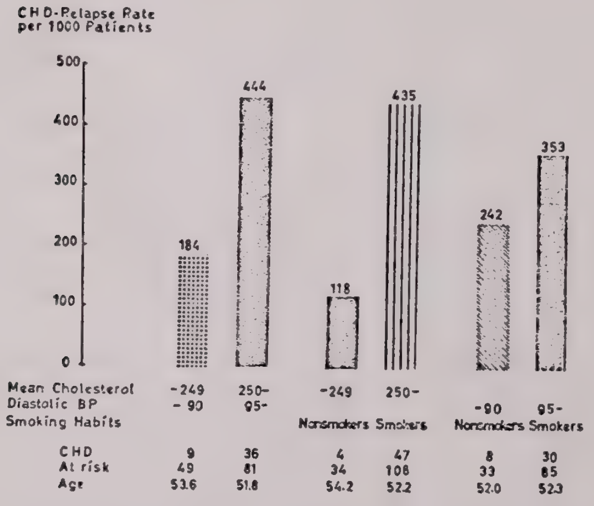


Fig. 3—Both groups. Age < 60. Coronary heart disease relapse rate in relation to combined risk factors.

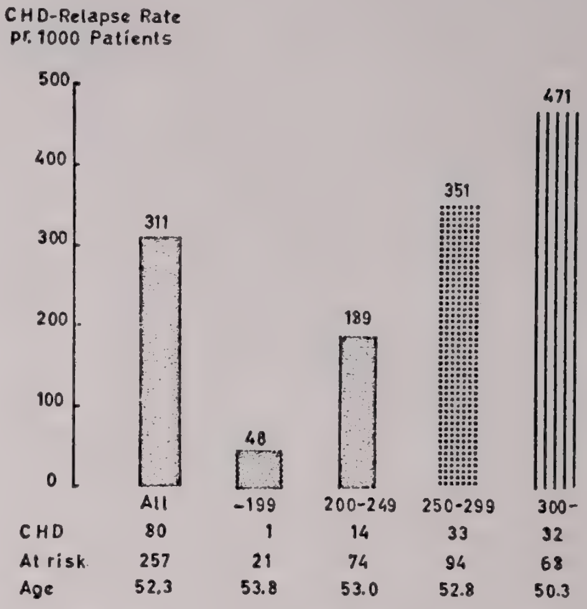


Fig. 4—Both groups together. Age < 60. Incidence of coronary heart disease to mean serum cholesterol level during the observation time.

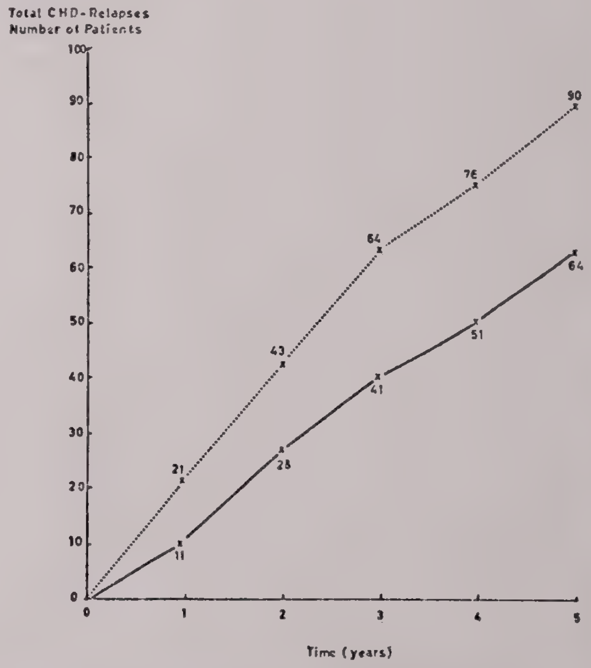


Fig. 5—Cumulated incidence of total coronary heart disease relapses.

cant ($x^2 = 10.00$, $p = .002$). In those with angina pectoris at the start of the trial the difference in the coronary heart disease relapse rate between dieters and controls was not statistically significant.

A significantly reduced relapse rate in the dieters as compared with the controls was found only in those with a normal relative heart volume at the time of the primary infarction.

The presence of a pathological electrocardiogram at the start increased the coronary heart disease relapse rate in both groups, especially the incidence of sudden death, which in both groups together was significantly higher when the electrocardiogram was pathological ($x^2 = 11.80$, $p = .001$). However, the reduction of the coronary heart disease relapse rate in the dieters was the same, whether the electrocardiogram at the start was normal or not.

Serum Cholesterol

Investigation of the relation of coronary heart disease relapse rate to the coronary risk factors which can be influenced by preventive measures, viz., serum cholesterol, blood pressure, and tobacco smoking, revealed that the serum cholesterol level was the factor which had by far the strongest influence on the coronary heart disease relapse rate.

When the groups were analyzed together for this purpose, it appeared that in the normotensives with a low serum cholesterol level and in the non-smokers with a low cholesterol level, the coronary heart disease relapse rate was significantly reduced as compared to the hypertensives with a high cholesterol level and to the smokers with a high cholesterol level (Figure 3). The respective tests of significance are: $x^2 = 8.05$, $p = .005$, and $x^2 = 9.99$, $p = .002$.

The correlation between the serum cholesterol level and the coronary heart disease relapse rate at age below 60 (both groups together) was striking (Figure 4). The data are as follows: a mean serum cholesterol value during the trial < 200, 200-249, 250-299, and $\geqq 300$ (mg per 100 ml) was associated with a total coronary heart disease relapse rate per 1,000 patients of 48, 189, 351, and 471 respectively.

In the patients who had overcome their previous myocardial infarction with no obvious signs and symptoms of heart disease, that is, without angina pectoris and with a normal heart volume and a normal blood pressure, a highly significant difference between the diet group and the control group in the total coronary heart disease relapse rate was found ($x^2 = 10.15$, $p = .001$).

Thus, in these subjects, who are believed to constitute the subgroups of the material most comparable with the general male population at the same age level, dietary reduction of plasma cholesterol proved to be most effective in the prevention of coronary heart disease relapses.

Conclusion

The effect of a plasma cholesterol lowering diet on the coronary heart disease relapse rate was studied for five years in a group of 206 male infarction patients and the results compared with those in another group of 206 patients who continued on a conventional diet.

The patients were allocated to the groups after a strictly randomized system, and the groups matched well.

The cholesterol lowering diet reduced the incidence of total coronary heart disease relapses.

There was a distinct difference in the effect on patients below the age of 60 and those of 60 and above. The difference was highly significant in the younger age group, but not in the older.

Sudden death occurred with an identical rate in the diet group and the control group, so that the significance applies to myocardial reinfarction — fatal and non-fatal — and to new cases of angina pectoris, but not to sudden death.

The most striking effect of dietary reduction of the plasma cholesterol was encountered in those who had recovered from their previous myocardial infarction with no obvious signs and symptoms of their heart disease. These subjects are thought to be most comparable to the general population.

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Continued to Page 1306.

Diet High in Unsaturated Fat[*]

A Controlled Clinical Trial

SEYMOUR DAYTON, M.D.[†]
MORTON LEE PEARCE, M.D.[‡]
Los Angeles, California.

It was known 10 years ago that certain dietary changes were capable of lowering the serum cholesterol concentration, and there was reason to suspect that such changes might retard the development of atherosclerosis and its complications. However, this inference was by no means a foregone conclusion, particularly as it applied to persons during and beyond middle age. The need for a clinical trial was apparent.

Domiciliary[§] Study

Use of the Domiciliary Unit in the Los Angeles Veterans Administration Center for such a trial readily suggested itself. This unit houses about 2,600 veterans, disabled or elderly, but ambulatory, with mean length of stay almost two years, about as long as in any large institution housing adults. In 1959 we began a controlled clinical trial of a diet low in saturated fat and supplemented with unsaturated fat, the trial ending in January, 1968. We are able to present data on morbidity and mortality which are complete and final, although not yet analyzed in full detail.

Age

The subjects were volunteers from the domiciliary population, aged 54 and above, with mean age 65.5 years. After baseline evaluation subjects were assigned at random either to a control diet or to the experimental diet. Ultimately started on the diets were 846 men, half in each group. Meals were served ad libitum, cafeteria style, from service lines which were separated physically. Service was controlled by color-coded meal tickets punched at each meal to provide individual attendance

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[*] Supported by the Veterans' Administration and by grants from the Arthur Dodd Fuller Foundation. Further documentation of the study is provided in earlier publications[1–7] and in a final report in press[8].

Presented at the Minnesota Symposium on Prevention in Cardiology, May 2-3, 1968 in Rochester, Minnesota.

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[§] See Test Your Word Score Page 1213.

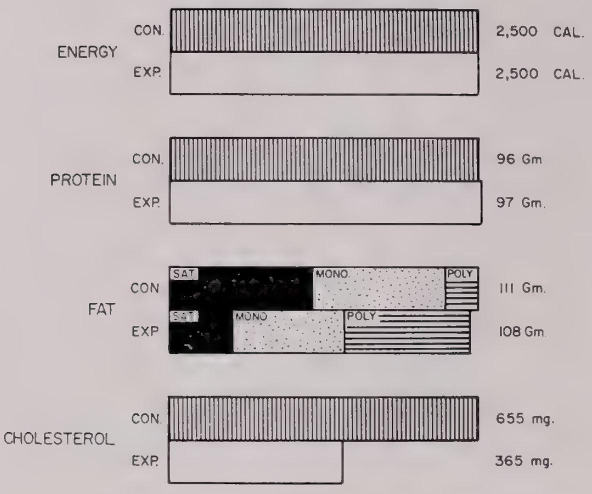

Fig. 1—Major nutrients of control and experimental diets; mean values shown are mean daily intakes for the individual receiving a typical tray at each meal.

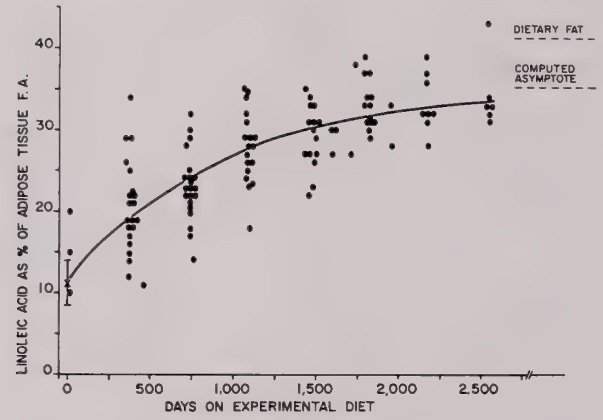

Fig. 2—Linoleic acid content of subcutaneous tissue in participants on the experimental diet. Subjects were selected for good adherence, defined as 80% or more of possible meals taken in the dining room. Values at day 0 are mean ± S.D. of 120 individual values.

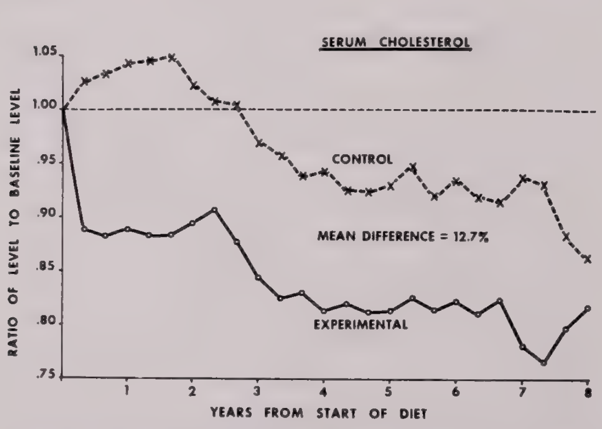

Fig. 3—Changes in serum cholesterol level of control and experimental groups. Each point is the mean of all values for the given interval.

records. The study was carried out on a double-blind basis.

The Controls

The control subjects received a conventional American diet of typical composition. The experimental diet was designed to simulate a conventional diet as closely as possible, in order to foster prolonged cooperation of even minimally motivated participants, while at the same time embodying maximum change in the character of dietary fat compatible with the objective of acceptability.

The Two Diets

Figure 1 summarizes the composition of the two diets as determined by analysis of weekly collections. They were comparable with respect to caloric content, protein, and the quantity of fat; however, the fat of the experimental diet was substantially more unsaturated, containing almost four times as much linoleic acid as the control diet and correspondingly less saturated fatty acid. The cholesterol content of the experimental diet was also reduced by nearly half in comparison with the control diet.

It was hoped and expected that no change in body weight would occur. Mean weight in both groups did in fact remain within 2% of the starting levels, although some individuals showed wide variations in both directions.

Adherence to diets in this institution is not enforceable and was imperfect, but it could be monitored. Mean adherence, as estimated by individual dining-room attendance, was approximately 80% for subjects of both groups during periods in which they were actually residing in the Center and participating in the study.

Figure 2 shows evidence confirming the fact that adherence estimates based on dining-room attendance are realistic. This is a plot of the rise in linoleic acid of subcutaneous fat in the experimental group, limited to subjects selected for good dining-room attendance, whose average attendance was 92% of the theoretical maximum. Although the rise was slow, the level approached the linoleic acid content of the experimental dietary fat, indicating that this was in fact the dominant fat source in these individuals.

The Results

Serum Cholesterol

Figure 3 demonstrates total serum cholesterol data over the eight-year period. The mean starting level was 233 mg/dl in both groups. The reason for the gradual decline in serum cholesterol in the control group is not known to us. We take the difference between the two groups as reflecting the net effect of the experimental diet. It amounted to 12.7%.

Table 1 bears a summary of data concerning comparability of the two groups in regard to factors which might have influenced the outcome of the study. We did not attempt to evaluate ethanol intake or exercise, assuming that meaningful quantitation of these would be out of the question. With regard to those factors shown, randomization of the subjects was expected to render the two groups comparable, and it did so. Please note the indication, in the right-hand column, that the participants were not all free of overt atherosclerotic disease. In these characteristics, as in regard to the others, the two groups were comparable. The only identified difference was in a characteristic—severe baldness—which is not known to be related to atherosclerosis and which was included in our data collection as a whim.

Discharge and Withdrawals

Table 2 shows information concerning discharge from the institution and re-entry; there was a good deal of coming and going. As both groups were comparable in this regard, this undesirable mobility was not a source of bias in the clinical data.

There were (Table 3) differences in the rates of withdrawal from the study. Of the 422 control subjects, 58 (14%) withdrew, the commonest reason being an order for a therapeutic diet. The withdrawal rate in the experimental group was higher, but only in the first two years. The dominant reason for the higher withdrawal rate was dissatisfaction with filled milk, the product available to us

TABLE 1

Comparability of the Two Groups of Participants

Two groups comparable at start in regard to:	
Race	Serum cholesterol
Religion	Serum total lipid
Age	Smoking habits*
Height	Cardiac compensation
Weight	Previous angina pectoris
Time in Center	Previous myocardial infarction
Systolic BP	Peripheral arterial occlusion
Diastolic BP	Aneurysm
Diabetes	Previous cerebral ischemia
11 ECG categories	Previous cerebral infarction
11 drugs	Previous cerebral hemorrhage
Corneal arcus	CNS function (8 categories)
Xanthomata	Other atherosclerosis
Different in regard to:	
Severe baldness (Control > Experimental)	

*Distribution of numbers of cigarettes per day differed, but there was little difference in total amount of cigarette smoking.

TABLE 2

Discharges from Center and Re-entries

Year	Number of Discharges		Number of Re-entries	
	Control	Exp't'l	Control	Exp't'l
1	136	138	20	20
2	75	66	41	39
3	41	66	33	40
4	38	35	31	24
5	26	30	14	15
6	20	23	10	22
7	14	16	8	5
8	6	4	4	6

TABLE 3

Withdrawals from Study

Year	Number	
	Control	Experimental
1	24	69
2	16	24
3	8	9
4	5	4
5	1	3
6	2	3
7	1	2
8	1	3
	—	—
Totals	58	117

TABLE 4
Major Cardiac and Cerebral Events

	Number of Men	
	Control	Experimental
Definite Myocardial Infarction, overt or silent	44	35
Sudden Death	27	18
Definite Cerebral Infarction	22	13
Definite MI—overt and/or Sudden Death and/or Definite Cerebral Infarction	83	52

TABLE 5
"Hard" Events (Non-fatal and Fatal)

	Number of Events*	
	Control	Experimental
Definite myocardial infarct, by ECG only	4	9
Definite myocardial infarct, overt	47	33
Sudden death	27	18
Definite cerebral infarct	25	13
Ruptured aneurysm	5	2
Amputation for gangrene	5	7
Miscellaneous	6	3
Total	119	85

*Including multiple events in individual subjects.

TABLE 6
"Soft" and Indefinite Events

	Number of Events*	
	Control	Experimental
Possible angina pectoris	6	5
Definite angina pectoris	10	11
Possible myocardial infarction	7	10
Probable myocardial infarction	4	3
Possible cerebral ischemia	7	5
Definite cerebral ischemia	8	5
Possible cerebral infarction	2	2
Asymptomatic peripheral occlusion	14	13
Intermittent claudication	11	13
New aneurysm	1	3
Totals	70	70

*Including multiple events in individual subjects.

in the early part of the study being of variable quality. Because of the differential in drop-out rates, any stratification of outcome data based on this characteristic would involve some risk of bias.

Double-Blind Study

The trial was double-blind. As a check on the integrity of this feature insofar as the medical staff was concerned, our three clinic physicians were asked, during the seventh year of the study, to guess at the diets of the subjects at 229 consecutive examinations. In the 104 instances in which an opinion was ventured, only 53 cases were correctly classified: a number compatible with random guessing. Our doctors thus displayed a gratifying degree of ignorance on this point.

Mortality

Men in the Center and in the study had electrocardiograms done, were re-examined annually, and were seen by our staff on the occasion of any hospitalization. At the end of the study, a search was conducted through the Veterans Administration Central Office for death certificates of men who were out of the Center and whose status was unknown. Completeness of mortality checks through the Veterans Administration is known to exceed 95%. Since the majority of our subjects who died did so in our Center, mortality ascertainment is estimated to be about 99% complete. We had no systematic morbidity surveillance for men once outside the Center, but some non-fatal events outside the Center came to our attention in various ways. Regardless of the place of a clinical episode or a death, it was recorded as representing an atherosclerotic event only if it met previously established criteria to the satisfaction of both of the authors. Unsupported death certificate diagnoses and unsupported diagnostic statements of physicians were not accepted. The autopsy rate for deaths within the Center was 80%, and for all deaths 65%.

Major Cardiac and Cerebral Events

The following data include every man who was ever assigned to diet regardless of his subsequent status. Furthermore, all subjects are followed to the end of the trial or to death, if earlier, regardless of non-adherence, regardless of subsequent withdrawal, and regardless of absence from the Center.

Table 4 presents data on the chief end points of the study. Myocardial infarctions, sudden deaths, and cerebral infarctions were all less numerous on the experimental diet. None of these individual differences are significant, but a combined look at disabling or fatal coronary and cerebral events, shown at the bottom of the Table, yields a difference which is significant at the 99% confidence level. If silent myocardial infarcts are included, the difference becomes smaller than shown here but is still significant at the 98% confidence level.

Definite Events

Table 5 shows complete data on "hard" end points: that is, events ascertainable with, we believe, little diagnostic error. The difference in the two groups in regard to myocardial infarction is augmented when silent myocardial infarctions are excluded. Events in peripheral vascular sites were approximately equal for the two groups.

Indefinite Events

Table 6 shows data on "soft" events, such as angina pectoris, and a variety of episodes classified as "possibles" or "probables." No differences are apparent, either for individual categories or for totals.

Mortality data are shown in Figure 4, in terms of total numbers of deaths. Deaths attributed to atherosclerotic events ultimately numbered 70 in the control group and 48 in the experimental group, with a p value less than 0.05 by chi-square. When we look at total mortality, in the upper pair of curves, we find differences for the first three or four years nearly identical to the differences due to atherosclerotic events; however, the curves for total deaths converge in the latter part of the study. Of course, all mortality curves have to converge ultimately, particularly in elderly men, but this convergence occurs earlier than we would like to see it. We shall have to take a careful look at causes of death

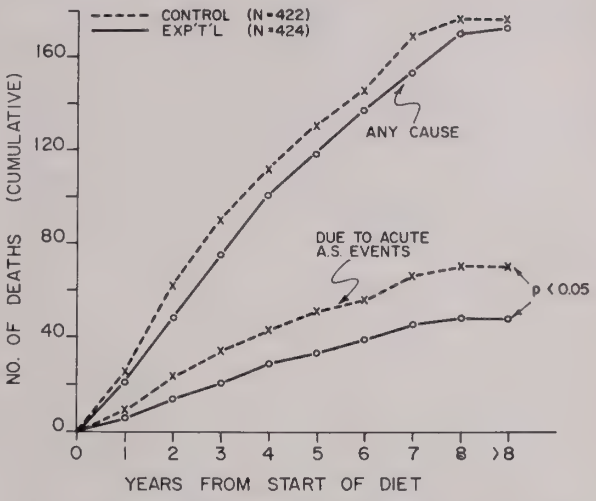

Fig. 4—Mortality data—total mortality and deaths due to acute atherosclerotic events. The latter figures include 10 control cases and 9 experimental cases in which other diseases contributed to the death. The number of cases in the trial beyond 8 years was small (56 in each group) and the duration of observation beyond 8 years was in no instance more than 4 months. Abbreviation: A.S. = atherosclerosis.

TABLE 7

Deaths Due to Acute Atherosclerotic Events

	Number	
Cause	Control	Experimental
Acute Myocardial Infarct	24	24
Sudden Death	27	18
Cerebral Infarct	9	3
Amputation	3	0
Ruptured Aneurysm	5	2
Intestinal Infarct	2	1
	—	—
Total	70	48

$p > 0.05$

TABLE 8

Deaths Due to Acute Atherosclerotic Events, Stratified by Age

	Cumulative Incidence, Per Cent*			
	Younger Stratum		Older Stratum	
Years in Study	Control	Exp't'l	Control	Exp't'l
1	2	0	3	3
2	5	1	8	6
3	7	2	12	9
4	10	4	15	13
5	13	5	18	15
6	15	7	20	18
7	20	8	25	24
8	21	11	29	24

*Computed by the life table method.[9]

in the last three years, but have not yet had the opportunity.

Fatal Atherosclerotic Events

Types of fatal atherosclerotic events are seen in Table 7. The difference in totals is contributed to by all categories except myocardial infarction, for which numbers of fatalities were equal.

Finally, Table 8 presents data on fatal atherosclerotic events stratified by age of the subjects at entry into the study. The cut point between the two age strata occurs at age 65.5. The data are computed by the life table method. Above the age of 65.5 there is little difference between the two diet groups, most of the difference occurring among men aged 54 to 65.

Conclusions

In summary, we have completed a double-blind clinical trial of a diet low in saturated fat and high in unsaturated fat. The diets employed sustained a mean difference of 13% between serum cholesterol levels in the control group and levels in the experimental group, during periods in the Center. The subjects were men over 54 years of age, some of them with pre-existing complications of atherosclerosis. The experimental group had a significantly lower incidence of major atherosclerotic events during the study than did the control group. Furthermore, fatal atherosclerotic events were less numerous in the experimental group than in the control group. Most of this difference occurred in the younger subjects, aged 54 to 65 at the start of the study.

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Red Light

A young student nurse was taking a driver's license test. Accompanied by a state policeman, she drove through a red light without noticing.

"Young lady, what does a red light mean to you?" the trooper inquired sarcastically.

Quick as a flash she answered, "A bedpan!"*

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* Maxwell Droke: The Speaker's Handbook of Humor.

Thou shalt not covet, but tradition
Approves all forms of competition.—Clough

Changes of Diet and Risk Factors*

in the National Diet-Heart Study*

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LIFE-LONG LOW LEVELS of serum cholesterol are associated with low incidence rates of coronary heart disease. The question *behind* the National Diet-Heart Study[1] has been asked many times, and still is being asked: Will changing diet to lower the serum cholesterol level also lower the incidence of first clinical episodes of coronary heart disease among middle-aged men? It was estimated that tens of thousands of clinically healthy subjects would be needed in a five-year experiment. Such an experiment was too large, complex, and crucial to undertake without knowing if it could be done; therefore, the National Diet-Heart Study[1] was mounted to assess its feasibility. The study addressed itself to many problems of feasibility but only three will be considered here: (1) Will enough healthy, middle-aged men volunteer from the general public for a big diet study: that is, eligible volunteers, willing to change their habits and adhere to a prescribed dietary regimen? (2) What is the effect of the dietary prescription on levels of serum cholesterol and on other risk factors? (3) Is a parallel experiment practical on men in a mental hospital under well-controlled conditions? What are the responses of the free-living men as compared with the institutionalized men?

Design and Methods

Six research centers adopted a common protocol for studies in five metropolitan areas on volunteers from the general public; with the sixth center using mentally retarded patients at the Faribault, Minnesota, State School and Hospital. The entire study was double-blind, neither the subjects nor the staff knowing diet assignments or individual blood lipid responses. The principal end point criterion was change of serum cholesterol, and the only purposeful intervention was on the fat composition of the diet. Changes of other variables, such as body weight, blood pressure, and smoking, were observed and followed.

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*Presented at the Minnesota Symposium on Prevention in Cardiology, May 2-3, 1968 in Rochester, Minnesota.

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The Diets

Three diets were tested in all six centers: Two were designed to lower serum cholesterol; and the third, called "D," was planned as a control diet, almost like the U.S. diet. It was a failure and contributed few useful results. Compared to the usual U.S. diet, the two treatment diets, if eaten according to their design, would have cut the intake of saturated fats and of dietary cholesterol by 60 per cent, and raised polyunsaturated fat intake three or four times. One of the diets, termed "B," was designed to reduce total fat intake from a U.S. average of about 42 per cent of total calories to 30 per cent, and the other, termed "C," would reduce it to 35 per cent, both diets avoiding extreme food alterations. Although B and C were intended to be somewhat different, the serum cholesterol responses were essentially the same. Therefore the results are pooled here.

The Subjects

The subjects were clinically healthy men, 45 through 54 years old, eating average U.S. diets, purportedly willing and able to follow the dietary prescriptions. Data were collected on the subjects during screening examinations and a baseline period and were then used to classify the men into stratified, matched cohorts for random, blind assignment to experimental diets. Thus men were not allowed to choose among the three diets. Subjects and their wives were taught which foods to use and which to avoid. At first, after diet changes, the men returned frequently to the clinics to give blood samples and nutritional and clinical data; then the interval between visits was lengthened to eight weeks.

Results

Of the base populations first reached by mail, 11 per cent volunteered for the study. The volunteers were screened, and one third were excluded about two to one (23% and 10%) respectively for medical and nutritional reasons. Approximately eight per cent of the men withdrew before the start of assigned diets, leaving 60 per cent of those examined to be randomized: about 1200 men in five cities and 220 at Faribault. Of those, 12 per cent dropped, or were dropped, from the study in the course of a year; the highest loss rates being early in the year.

The mean baseline serum cholesterol concentration for men in all five cities was close to 230 mg/dl, and the means for the cities varied from 222 to 233. Faribault was low at 208 mg/dl. (Faribault dietary information available at the time was inadequate to explain that low level.)

There was a greater variation among Centers in the proportions of men, at baseline, with high serum cholesterol levels (280 to 350 mg/dl): from 20 per cent of men in one city to 7 and 8 per cent in two others, and 5 per cent at Faribault. These are important differences because baseline levels have been shown to affect serum cholesterol response to a specific diet change.[2]

Serum Cholesterol Changes

Table 1 shows the mean baseline serum cholesterol concentrations and changes for free-living subjects in all five cities together, and for Faribault. Serum cholesterol levels of free-living men on diets B and C fell from a baseline average of 230 to 204, a decrease of 26 mg/dl, or 11 per cent of baseline level. Faribault men on B and C diets went from their low mean of 208 to 172, a decrease of 36 mg/dl, or 17 per cent—considerably more than the free-living men, no doubt because their foods were almost fully controlled.

B and C diets depended heavily on special fat-modified foods made for the study; another

TABLE I

Mean Serum Cholesterol Concentrations and Changes
Diet-Heart Study First Year

	Five Cities			Faribault		
	Conc.	Change		Conc.	Change	
Diet	mg/dl	mg/dl	%	mg/dl	mg/dl	%
Baseline	230	—	—	208	—	—
B and C	204*	–26	–11%	172‡	–36	–17%
X	204†	–26	–11%	—	—	—

*612 men

†41 men—one city only

‡91 men

treatment diet, X, tested in one of the cities, did not. In the X diet the men used only foods available commercially, and their average decrease was identical to that of all free-living men on B and C, 26 mg/dl, or 11 per cent. But those men on the X diet did not do as well as their fellows in the same city on B and C. Hence special foods did help the subjects to reach lower serum cholesterol levels, though they were not essential for effective overall diet change. This is of interest in that suitable foods are becoming increasingly available to the public.

Influence of Weight

Two factors which affect serum cholesterol response to diet alteration are body weight change and baseline serum cholesterol level. With decreasing body weight serum cholesterol generally falls; with increasing weight it rises. Table 2 shows the influence of the baseline cholesterol level on response to what was probably the same average diet change. The third of the men with low initial levels, averaging 188, decreased 18 mg/dl, whereas the men in the upper third of the baseline distribution, averaging 268, had a decrease of 35 mg/dl. So, from the high third to the low, the response was half as great—35 to 18; yet the baseline serum cholesterol level was only 30 per cent less. The same pattern was observed at Faribault. Generally, there will be a much greater response to the same diet change from high-level men than from men who already are low.

Table 3 represents the calculated target serum cholesterol changes for the diets compared to those observed, for all B and C men in the five cities.[3] Faribault was close to the goal, as was expected because the men had access only to the meals served. The averaged calculated target for five cities was a decrease of 42 mg/dl, and the observed change was 26-27, or 63 per cent of target, a value that may be a good index of adherence to the prescription. There was some variation among the averages of the cities from 45 per cent of target to 83 per cent, even under the common protocol. However, that range would be less if the populations were corrected for "responsivity," due to their differing proportions of high and low-cholesterol men at the start.

TABLE 2
Mean Serum Cholesterol Changes, Baseline to 32 Weeks on Diet; Five Centers
Men Classified by Baseline Level

Baseline Class mg/dl	Mean Baseline mg/dl	Mean Change, mg/dl Diets B + C	Mean Change, mg/dl Diet D
All men	230	−26	−6
Under 210	188	−18	+3
210 to 241	226	−25	−4
242 to 349	268	−35	−13

TABLE 3
Calculated Target and Observed Serum Cholesterol Changes by Center

Center	Calculated Target Change mg/dl	Observed Change mg/dl	Relative Achievement of Target %
Five Centers	−42	−27	63
Center H	−44	−20	45
Center C	−41	−20	49
Center O	−42	−25	59
Center J	−40	−29	72
Center M	−45	−37	83

Discussion

How might these very real and significant changes, and the recorded variations in blood pressure and smoking, affect the overall risk of coronary heart disease? A rough approximation, entailing some dubious assumptions, is given in Table 4. At Faribault the lowering of serum cholesterol plus an unexplained 10 mm systolic blood pressure decrease, add up to a 47 per cent predicted decrease in risk. In the five cities, measured changes of systolic blood pressure and of serum cholesterol, plus reported changes of smoking habits during the experiment, add up to a predicted 34 per cent lowered risk. The predicted risk change was −41 per cent from the calculated target lowering of serum cholesterol, with no change of blood pressure or smoking.

Looking ahead a little, on the supposition that diet, serum cholesterol, atherosclerosis, and heart disease are indeed causally related, we might well be more concerned about the coronary heart disease incidence rates in our children when they reach our age than we are about our own generation. For, with the post-World War II opulence, a great many of these

TABLE 4

Approximations of Change of CHD Risk Status for
B & C Diet Groups
Diet-Heart Study, First Year

Assumptions:

1. Decreased risk factor levels are maintained long-term by men completing study.
2. Changes of risk factor levels change risk status to Framingham risk levels.
3. Body weight changes are too small to change risk status.

	Relative Risk Status Change from Risk Factors:			
Cohort	Serum Chol. %	Syst. B. P. %	Cig. Smoking %	Sum %
Faribault				
91 men completing study	–39	–8	?	–47*
Five Cities				
612 men completing study	–28	–2	–4	–34*
Target	–41	0	0	–41

*Inclusion of drop-outs decreases sum of risk change by 4%.

young people will have been exposed to a richer diet for more years than we were, as well as to more cigarette smoke. So we may have even higher incidence rates, and at younger ages, than are now current—unless the necessary is done soon.

Success of any major public health effort in this direction, whether in the form of a mass field trial or a generalized attempt to change food habits, must depend heavily on an informed public and on full knowledge and collaboration of the medical community, and of major segments of the food industry.

Conclusions

Reverting to the National Diet-Heart Study and its assessment of feasibility of definitive experiments on the effect of diet alteration on CHD incidence, the Study Group concludes that, given a reasonable study design: (1) Enough eligible men would volunteer from the general public to yield the numbers of subjects needed for a definitive experiment. (2) Drop out rates and adherence to dietary prescriptions would be tolerable. (3) The probability of lowering incidence of coronary heart disease significantly—perhaps by 30 per cent—in free-living male volunteers is high enough to warrant a mass field test of the prevention hypothesis. That probability is higher for men at relatively high risk, since their potential for improvement is greater than for men at lower risk. (4) Institutional studies can be expected to define more exactly the changes and their results than can studies on free-living subjects, but would probably leave unanswered the question of what alterations might be achieved by the general population.

Recommendations

Key recommendations of the Final Report on the study are that: (1) Definitive experiments on coronary heart disease and diet, and possibly other risk factors, should be planned and put in operation as soon as possible. (2) Subjects should be randomized between control and experimental cohorts. (3) The studies should be done on free-living subjects and possibly on institutionalized subjects; concentrating on the coronary-prone because they represent the major public health program, and because their risk status should change more for a given diet change than that of other men, thus minimizing the number of subjects required. (4) Concurrent studies on primary and secondary prevention should be considered.

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Derivatively Speaking

Obese—from Latin *obesus* (having eaten itself fat).

Blood Lipids and Primary Coronary Events*

The Effect of Diet Modification

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When this study was started about ten years ago there already was much epidemiological and other indirect evidence to favor the hypothesis that the incidence of coronary heart disease could be decreased by a suitable change in the fat composition of the diet. It had been found that in populations experiencing a high incidence of coronary heart disease, the serum cholesterol values tended to be high along with the dietary intake of saturated fats. Furthermore, it had been demonstrated that the serum cholesterol level could be influenced by diet, particularly by the quality and quantity of fats. However, the hypothesis had not yet been tested by direct experiments in which the diet of a population was changed to satisfy the requirements of the hypothesis, and in which the development of manifestations of coronary heart disease had been observed over a sufficiently long period. We felt that the feasibility of dietary prevention of coronary heart disease could be conclusively determined only by means of such an experiment.

Coronary heart disease and its ultimate con-

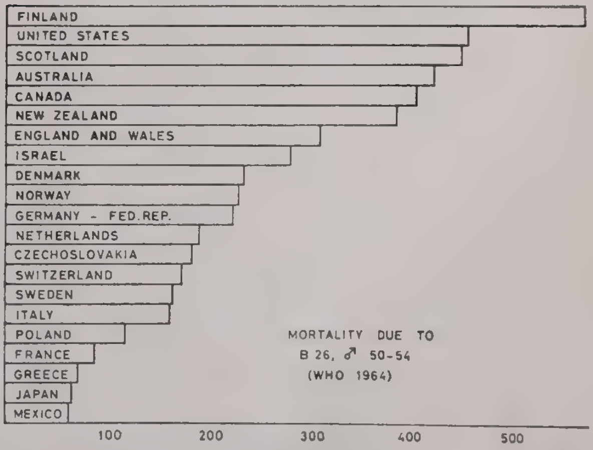

Fig. 1—Mortality (per 100,000 annually) of men aged 50 to 54 due to arteriosclerotic and degenerative heart disease.

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[*] Presented at the Minnesota Symposium on Prevention in Cardiology, May 2-3, 1968 in Rochester, Minnesota.

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sequence, coronary death, are quite common in the United States. Figure 1 shows, however, that they are still more common in Finland. This diagram shows the mortality among middle-aged men in a number of countries due to category B 26 of the International Classification of Diseases. Category B 26, although not exactly synonymous with coronary heart disease, is the closest approach to it in official vital statistics. Figure 1 shows the mortality within only one narrow age class. Figure 2 indicates that much the same relative differences prevail in other age classes as in Finland, the United States, England, Sweden, France and Japan. These facts explain why our study is being carried out in Finland.

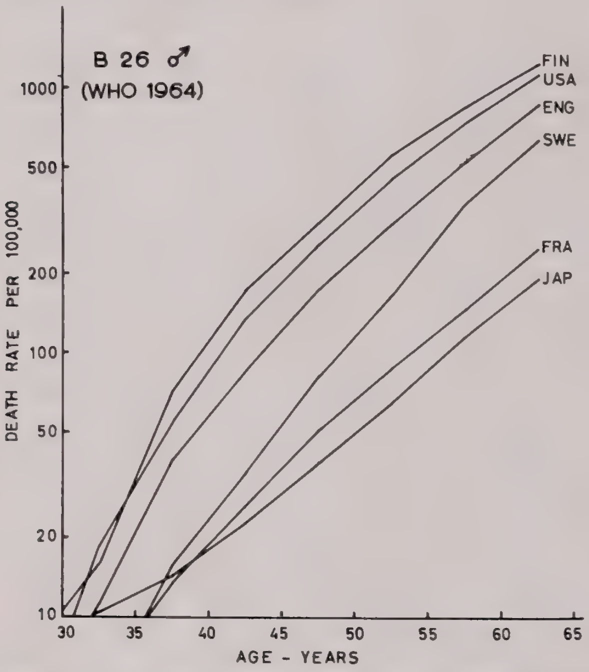

Fig. 2—Age-specific mortality (per 100,000 annually) due to arteriosclerotic and degenerative heart disease. (FIN = Finland, ENG = England, SWE = Sweden, FRA = France, JAP = Japan)

Plan of Study

Our study was started in two mental hospitals near Helsinki in 1958 (Figure 3). One of them, designated Hospital N, had the diet changed so that a large part of saturated fat was replaced by soybean oil, whereas the other hospital, Hospital K, was kept as the control without any intentional dietary change. In early 1965, when the experimental diet had been in use in Hospital N six years, the roles of the hospitals were reversed by returning Hospital N to the normal diet and by placing Hospital K on the experimental diet. It is our intention to continue the experiment according to this cross-over design for a number of years.

This report deals mainly with the observations made during the first six years of the experiment and on male patients only.

The patients ranged in age from 34 to 64 years at the beginning of the experiment. All patients within this age range who were not mentally or physically heavily incapacitated were included.

Although mental hospital populations generally do not change rapidly, a certain number of subjects were lost in both hospitals through discharges to other hospitals or home or through deaths. The average annual loss of subjects was about 15 percent. In order to keep the number of subjects in the study approximately constant, new subjects were added annually. The total number of male subjects studied during the first part of the experiment was 327 in Hospital N and 254 in Hospital K.

Diets

At the start the diets in both hospitals were similar and typical of Finnish diets. They contained large quantities of fat of the saturated type derived mainly from whole milk and butter. The total fat contents of the diets were about 33% of the food energy, and more than one half of this came from milk fat, which contributed about 17% to the total food energy.

Change from Milk Fat to Vegetable Fat

On January 1, 1959, the diet in Hospital N

	HOSPITAL N	HOSPITAL K
1958	NORMAL DIET	NORMAL DIET
1959	EXPERIMENTAL DIET	NORMAL DIET
1960		
1961		
1962		
1963		
1964		
1965	NORMAL DIET	EXPERIMENTAL DIET
1966		
1967		

Fig. 3—Design of our study.

was changed in two principal respects. First, whole milk was replaced by an emulsion of soybean oil in skim milk, and second, butter and ordinary margarine were replaced by a new brand of margarine containing considerably more unsaturated acids than commercially available brands. The effect of these changes was that the milk fat present in the original diet was almost totally replaced by vegetable oils, mainly soybean oil.

Increase in Polyunsaturated Fats

Figure 4 shows how the dietary change in Hospital N increased the quantity of polyunsaturated fatty acids about three-fold and decreased that of saturated acids by one half, and thus rendered the dietary fatty acid composition of the experimental hospital greatly different from that of the control hospital. This diagram shows the mean fatty acid compositions of the hospital diets during the whole six-year period. (S = saturated, M = monounsaturated, P = polyunsaturated). The total content of fat was slightly higher in Hospital K, but it had been so before the experiment started and we could not change it.

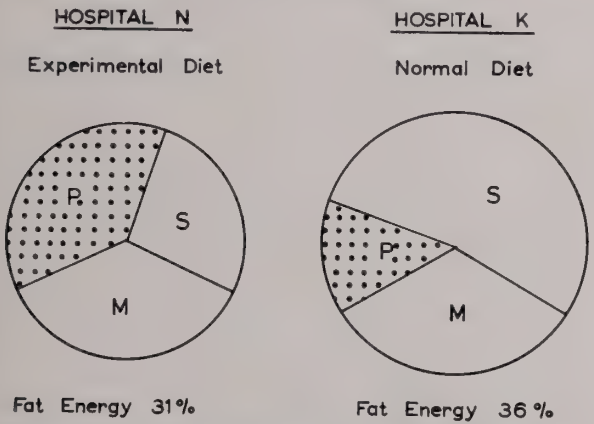

Fig. 4—Fatty acid compositions of the diets in the two hospitals (S = saturated, M = monoethenoid, P = polyethenoid)

Blood Lipids

Blood samples for lipid determinations were collected from the study groups at least once a year, and from these samples cholesterol levels were determined. Triglycerides and lipid phosphorus were determined less frequently.

Serum Cholesterol

The mean serum cholesterol levels in the two hospitals are shown in Figure 5. The initial cholesterol appeared to be somewhat higher in Hospital K; the difference, however, was not statistically significant. It could be accounted for, at least partly, by the higher content of the dietary fat and cholesterol in Hospital K. The change of the diet caused an early fall in the cholesterol value in Hospital N, but mean cholesterol values remained stable during the six years of the experiment.

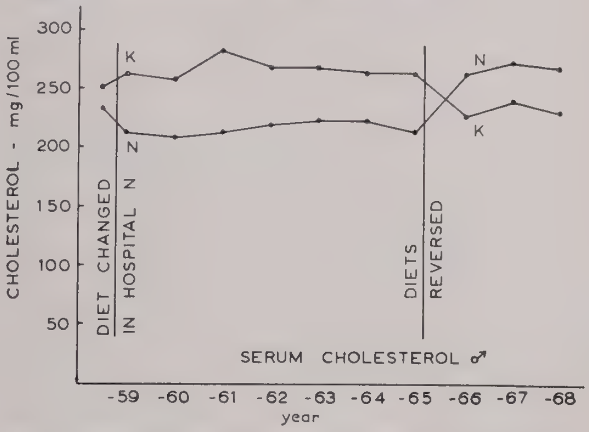

Fig. 5—Mean cholesterol levels of men in the two hospitals.

The average cholesterol level during the six years after the change of the diet was 217 mg in Hospital N and 268 mg in Hospital K: a difference of about 50 mg between the levels of the two hospitals; and this difference was statistically highly significant at all times after the change of the diet.

The reversal of the diets in the cross-over design in 1965 brought about a decrease of cholesterol in Hospital K and an increase in Hospital N, as expected. The difference of the cholesterol levels now reversed itself, though the magnitude of the difference was somewhat smaller in this second phase, namely, 35 mg vs. 50 mg.

Triglyceride and Lipid Phosphorus

Serum triglyceride and lipid phosphorus determinations showed that these lipid fractions were also lower in Hospital N where the diet had been changed. The differences, however, were smaller for these two lipid fractions than for cholesterol. Furthermore, the triglyceride values were characterized by a high coefficient of variation. Consequently, of the three serum lipid values cholesterol obviously was the best discriminator between the two subject groups ingesting different diets.

Adipose Tissue

The composition of animal adipose tissue is influenced by diet; that the same holds true in the human species has recently become evident. Human adipose tissue can be examined by the needle biopsy technique followed by gas-liquid chromatographic analysis of the fatty acid composition of the sample. Such studies also afford a useful check on the adherence to the diet and on its long-range effects, as the composition of the adipose tissue changes slowly.

Samples of subcutaneous adipose tissue were taken from a group of patients in each hospital near the end of the first part of the experiment. All these subjects had been in the hospital at least five years.

Figure 6 shows the approximate fatty acid composition of subcutaneous adipose tissue of subjects in the two hospitals. Great differences were found. The adipose tissue of the experimental group contained much more polyunsaturated fatty acids, mainly linoleic acid, and much less saturated acids. In this group the myristic* acid and the palmitic acid were also considerably lower. The stearic acid contents were practically identical in both hospitals as were the contents of oleic acid. A comparison of the fat composition of the diets indicated that the adipose tissue reflected the fatty acid composition of the diet.

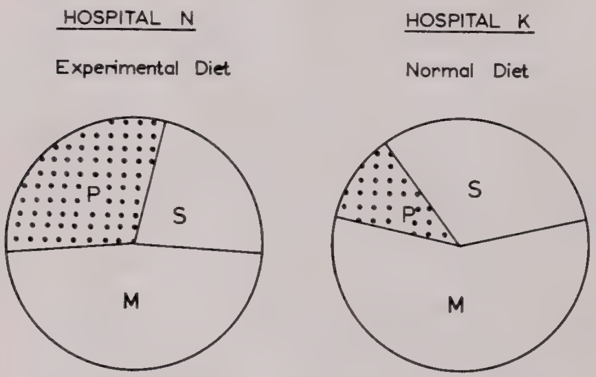

Fig. 6—Mean fatty acid compositions of adipose tissue of men in the two hospitals (S = saturated, M = monoethenoid, P = polyethenoid)

The changes of the adipose tissue after the reversal of diets are shown in Figure 7. Only two fatty acids, linoleic and myristic acids are included: the two with the greatest relative differences between the two groups. It is seen that two and a half years after the reversal of the diets, the fatty acid compositions had also become reversed, although not completely.

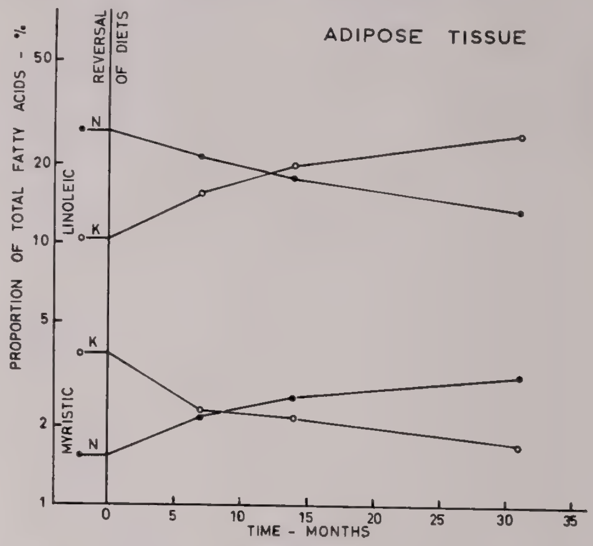

Fig. 7—Changes in linoleic and myristic acid contents of adipose tissue in the two hospitals after the reversal of the diets.

The Electrocardiogram

The assessment of incidence of coronary heart disease in these two groups was the most important aspect of our study. It was also the most difficult. Despite attempts to establish standardized systems of criteria for the diagnosis of coronary heart disease, no fully satisfactory system has been developed.

Furthermore, in our work we had to pay attention to special characteristics of our study groups, which consisted of psychiatric—mainly schizophrenic — patients. In such patients the response to painful stimuli is often considerably diminished; hence the symptomatology of coronary heart disease may be exceptional. The incidence of painless heart attacks is high and there is an almost complete absence of anginal syndrome. The incidence of sudden death is also high.

Chief reliance in this study was placed on electrocardiography. Electrocardiograms were taken from the study groups once a year. In the classification of records, the "Minnesota Code" was used. This system provides a method for a relatively objective classification of electrocardiographic findings. All records in this study were read and coded by the same member of the team and without knowledge from which hospital the tracing came.

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*See Test Your Word Score Page 1213.

The incidence of electrocardiographic patterns presumably due to coronary heart disease, based on different criteria, is shown in Table 1. Two criteria having different levels of discriminative power and based directly on the Minnesota Code are shown, first, Q items and, second, Q, S-T and T items, combined into one category. Furthermore, a system of criteria used by Epstein in the Tecumseh Study is also included at two levels of discrimination.

The first column shows the number of patients initially free from the respective electrocardiographic sign; the second shows the number of patients developing the sign some time during the six-year period of observation. The third column shows the annual incidence rate per one thousand, and in the extreme right column we see the significance of the difference between hospitals determined by means of the X^2 test. The data presented in this table demonstrate that the incidence of electrocardiographic patterns presumably due to coronary heart disease was, by all these criteria, markedly and significantly lower in Hospital N. The difference between the hospitals in the incidence of changes was greatest when the more rigorous criteria were applied; but even the use of the milder criteria revealed significant differences.

We also have electrocardiogram data (Table 2) for the first two years after the reversal of the diets. The figures are too small to be conclusive, but they point in the expected direction.

Coronary Mortality

Coronary deaths have also been studied. For this three criteria were adopted: 1, sudden unexpected death for which no other cause was evident; 2, slower death with objective diagnostic evidence of coronary heart disease, such as typical electrocardiographic changes and increase in serum transaminase or other enzyme activity; or 3, death associated with autopsy findings of occluding or nearly occluding thrombi in coronary arteries or of recent myocardial infarction.

A comparison of mortality between the two hospitals indicates that while the non-coronary mortality figures were practically identical, the coronary mortality was lower in Hospital N. However, the mortality figures were too small to permit statistically valid conclusions.

Incidence of Coronary Heart Disease

Table 3 shows the total incidence of coronary heart disease diagnosed from electrocardiographic criteria and coronary death. The electrocardiographic criterion used was "probable coronary heart disease," Classes I and II, according to Epstein. This was a criterion of medium discrimination, which, we felt, was

TABLE I

Incidence of Certain Electrocardiogram Signs

ECG Signs	Patients Initially Healthy	 Developing sign	Incidence Rate per 1000	Significance of Difference
Q Changes				
Hospital N	282	0	0	< 0.01
Hospital K	219	7	7.9	
Q,S-T, T Changes				
Hospital N	269	25	22.8	< 0.02
Hospital K	210	35	43.4	
CHD, "Probable I"				
Hospital N	284	0	0	< 0.02
Hospital K	218	6	6.7	
CHD, "Probable" and "Suspect"				
Hospital N	270	25	22.7	< 0.02
Hospital K	209	35	44.0	

TABLE 2

Incidence of Electrocardiogram Signs of Coronary Heart Disease

	No. of cases		Rate per 1000	
	N	K	N	K
1959 - 65	12	25	10	29
1965 - 67	9	5	25	20

Incidence of electrocardiographic signs ("Probable coronary heart disease" according to Epstein et al.) before and after the reversal of the diets.

TABLE 3

Incidence of Coronary Heart Disease

	Hospital N	 K
Patients at Risk	313	241
CHD: ECG or Death	17	30
Annual Incidence Per 1000	14.4	33.0

Significance of Difference:

$X^2 = 7.75 \quad P < 0.01$

Incidence of coronary heart disease judged by electrocardiographic signs and coronary death.

closer to the true incidence than the stricter criteria based on Q patterns only.

Table 3 also shows that the incidence of coronary heart disease was significantly lower in Hospital N but does not reveal the true incidence of coronary heart disease in our study groups. Cases with angina as their only manifestation were missed, as its diagnosis in groups like ours would be very difficult. Furthermore, non-fatal attacks of myocardial infarction which did not develop electrocardiographic changes permanent enough to be detected at the next recording period (which may have taken place several months later after the event) were also missed. But these cases were probably not numerous.

For the purpose of this study, however, it was immaterial whether we diagnosed all new cases of coronary heart disease or only a certain fraction if it was equal in both hospitals.

Conclusion

Was the diet really responsible for the lower incidence of coronary heart disease in the experimental group? The design of our experiment deviated from the ideal in that the two study groups were not drawn from the same population by a random allocation. We have tried to assess their comparability with reference to a number of known risk factors such as age, prevalence of hypertension, smoking habits and the electrocardiographic status at entry to the study. The differences seem insufficient to account for the marked difference in the incidence of coronary heart disease. The only significant factor which reasonably explains the lower incidence in the experimental group is the cholesterol-lowering special diet; however, we prefer to regard this conclusion as preliminary, until more data from the second part of the experiment become available.

The Mind and Food

Worry and anger may bring about constipation due to the injury to the digestion system. Fears and worry may also produce nausea and other upsets, according to an announcement by the Academy of Medicine.

At mealtime we should observe good eating habits and try to remain tranquil and having pleasant thoughts. By eating slowly and thoroughly masticating our food we would greatly improve and help in the digestion of our food.

Ulcerated patients should beware of highly emotional states like anger, resentment, hostility, anxiety, worry and arguments, as these cause disorders of stomach activity.*

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*Culinary Almanac, 1949.

Oddities

Mining-camp doctors encountered odd afflictions made worse by neglect. In 1867 Dr. Glick removed a 70-foot tapeworm from Luke Byrne, a Bear Gulch, Montana, miner after he had treated himself with purgatives, vermifuges, and whiskey until he was too weak to dig. Dr. Thomas Reece of Helena traveled to nearby Unionville to treat a man and his wife who were seriously ill. He inquired as to what they had eaten and was told ham. Taking the ham to his office, he placed it under his microscope and discovered trichinae in the fibers. Soon everybody in town filed in to look at the specimens. Sales of ham ceased in Helena, and the butchers threatened to run the doctor out of town.*

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*Richard Dunlop: Doctors of the American Frontier, 1965.

Eat in measure and defy the doctor.—Culinary Almanac.

A Lipid Clinic

Preliminary Observations*

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In the summer of 1967 a lipid clinic was started at the Mayo Clinic. Our colleagues in internal medicine referred patients to us with elevated values for plasma lipids, and we have now seen several hundred of them. Such a patient's lipid abnormality is classified by determinations of plasma cholesterol, triglyceride and lipoprotein. A dietary history is obtained, and factors such as intake of alcohol, family history, other pertinent diagnoses and laboratory findings, presence of xanthomatoses or atherosclerotic disease are also noted. The treatment is individualized and depends not only upon classification of the lipid disorder but upon the other features just mentioned.

Causes

The clinical application of lipidology is very different from the epidemiologic application. The first difference is that elevation of values for lipids suggests to the clinician a variety of possible causes for which he must search.

Hypercholesteremia

Hypercholesteremia in the presence of normal values for triglycerides, that is, hyperbetalipoproteinemia or Fredrickson's Type II lipid disorder,[1] is observed in three clinical settings. It may be associated with a very high dietary intake of saturated fats and cholesterol and sometimes with obesity; appropriate dietary counseling is likely to be helpful. Hypercholesteremia can be the result of a familial disorder in which there are predictable hereditary features. This form is only partially affected by diet, and even the use of a full range of drugs may not bring the content of cholesterol in the plasma to normal. Finally, hypercholesteremia can be secondary to specific diseases, such as myxedema or biliary cirrhosis.

Hypertriglyceridemia

There is another family of common lipid

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*Presented at the Minnesota Symposium on Prevention in Cardiology, Rochester, Minnesota, May 2 and 3, 1968.

†Mayo Clinic and Mayo Foundation: Section of Medicine.

‡Mayo Clinic and Mayo Foundation: Section of Biochemistry.

disorders in which values for triglycerides are elevated and in which, to a lesser extent, those for cholesterol may be elevated. These disorders seem frequently to be linked with carbohydrate intolerance or an excessive intake of alcohol and with obesity; it is quite unlikely that excessive dietary fat alone is responsible for them. It has been shown that carbohydrates, and especially sugar, will cause an increase in endogenous triglycerides in susceptible patients.[2] By measuring only blood cholesterol, or by not understanding the fundamental metabolic difference between hypertriglyceridemia and hypercholesteremia, it is possible to elevate the patient's blood lipids still more by substituting sugar and other carbohydrates for fat in the diet.

Value of Classification

The clinician, therefore, needs a specific assay of the lipid abnormality if he is to treat the patient rationally and successfully. A patient with definite and reproducible hypercholesteremia might be optimally treated with only *one* of the following programs, depending on the cause of the increase in cholesterol and whether or not it is associated with endogenous hypertriglyceridemia:

> A fat-restricted diet; a sugar-restricted diet; reduction in weight; cessation of intake of alcohol; diet and cholestyramine; diet and clofibrate; diet and nicotinic acid; treatment of myxedema—or other disease to which the hyperlipidemia may be secondary.

Because of this diversity, individual classification is of value. The following preliminary data come from the analysis of records of 100 consecutive patients as well as from some follow-up information that was available at the time of study.

Distribution of Types

No patients who had Type I hyperlipidemia were seen. Roughly half had Type II, hyperbeta-lipoproteinemia (increased content of cholesterol with normal values for triglycerides). The remaining half represented problems of very low density lipoprotein (VLDL) excess (endogenous triglyceride excess); three patients had a typical broad-band, beta pattern (Type III); and 16 had a variant of this with very low density lipoprotein excess carried on a narrow beta band. Twenty-seven patients had typical prebeta-lipoprotein excess (Type IV); six had prebeta-lipoprotein excess plus chylomicronemia (Type V) and three patients had mixtures of beta and prebeta-lipoprotein excess.

Characteristics of Types

Some differences of the types are apparent in Table 1. Although the ranges in age are similar, the distribution according to sex tended more toward females in Type II disorders and toward males in the other types. Mild fasting hyperglycemia or abnormal results of tests of glucose tolerance were noted in about 40% of those with an excess of triglyceride, but in none of the patients with Type II disorder. Obesity was twice as common among those who had excess of triglyceride (Types III, IV and V) as compared to those in the Type II group.

TABLE I

Lipoproteinemia: Characteristics in 100 Patients*

	II	III	IV	V
Average age (years)	53	54	53	48
Range	5-86	39-67	38-74	36-60
Sex, %				
Male	36	74	82	84
Female	64	26	18	16
Diabetes (borderline), %	0	42	30	50
Obesity, %	44	90	70	100

*Type I lipoproteinemia not encountered in this series.

Other areas of differences between patients with Type II (with normal values for triglycerides) and the types with increased triglycerides are seen in Table 2. Treatment by diet achieved roughly an average reduction of 15% in the content of cholesterol in all types; however, dietary treatment lowered values for triglycerides much more successfully than it did those for cholesterol. Whereas lipid values of only 12% of patients with the Type II disorder were restored to normal, roughly half of the patients who had excess of triglycerides (Types III, IV and V) became normal by means of dietary treatment alone.

Our experience leads us to believe that there are two basically different common lipid disorders. One group, comprising about one half, is characterized by hypercholesteremia with a normal content of triglycerides (Type II). The majority of patients who have the Type II disorder appear to have acquired their abnormality apparently because of inability to maintain normal values for lipid in the face of a high intake of saturated fats or cholesterol, or

TABLE 2

Lipoproteinemia: Differences Between Type II and Other Types*

	II	III	IV	V
Cholesterol before Rx, mg/100 ml				
Mean	370	315	343	310
Range	280-804	211-506	183-372	228-408
Triglyceride before Rx, mg/100 ml				
Mean	106	386	264	828
Range	60-202	135-1820	141-790	488-1952
Reduction by diet				
Cholesterol, %	14	21	13	10
Triglycerides, %	2	70	57	30
Followup, % of patients	38	47	26	67
Levels restored to normal, %	12	67	43	50

*Type I lipoproteinemia not encountered in this series.

occasionally because of some specific disease such as myxedema. Some of the patients with this disorder have familial hypercholesteremia; one third of our group had a family history of lipid abnormality. The familial disorder is resistant to treatment and usually requires both dietary and drug therapy (nicotinic acid or cholestyramine). The "acquired" types are more easily controlled by means of dietary treatment alone, or by specific treatment in cases in which the disorder is secondary to diseases such as myxedema.

The other groups of lipid disorders (Types III, IV and V) are those of excess of endogenous triglyceride, carried as a very low density lipoprotein in several different locations on the lipoprotein strip—either on a narrow beta band, a broad beta band or in the prebeta position with occasional spillover into the chylomicron band. These groups appear to be peculiarly responsive to reduction in weight and to the intake of alcohol or sugar. In the instances in which dietary treatment does not suffice, drug treatment (clofibrate) usually is very effective.

References

1. Fredrickson, D. S., Levy, R. I. and Lees, R. S.: Fat Transport in Lipoproteins—An Integrated Approach to Mechanisms and Disorders. New Eng J Med 276: 34, 94, 148, 215, 273, January 5, 12, 19, 26 and February 2, 1967.
2. Kuo, P. T. and Bassett, D. R.: Dietary Sugar in the Production of Hyperglyceridemia. Ann Intern Med 62:1199, 1965.

Anatomy #101

"The supreme moment had arrived for him; but it was indeed a faltering instant. He had waited ten years to commit this act and he had bolstered his courage time and again, so that he might not fail; so that nothing would go astray; now he found himself nervous!

His hand trembled as his fingers coiled themselves around the cold steel handle of his knife. He had fashioned this knife himself, and had sharpened and resharpened it while he waited for this scene in his life's drama.

"His lips set in the grimness of a murderer, he poised his knife for this, his first thrust on flesh; his first but not his last. He recalled the hand once, and then, determined he brought steel against flesh!

"The sickly feeling all gone, he now felt courageous enough to give a raucous laugh . . . the freshman medical student had started his first dissection."

(D.E.B. in Journal Association Medical Students)*

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*Saul, F. William, M.D.: Pink Pills for Pale People, 1949.

WHAT'S
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THE WEAKER
SEX?

OFTEN... HER LOWER G. I. TRACT

Psycho-abdominal Distress: Frequently Female

Women aged 15 to 45 appear to be more prone than men to bloating, cramping pain of stress-related intestinal disturbances such as irritable or spastic colon.[1,2]

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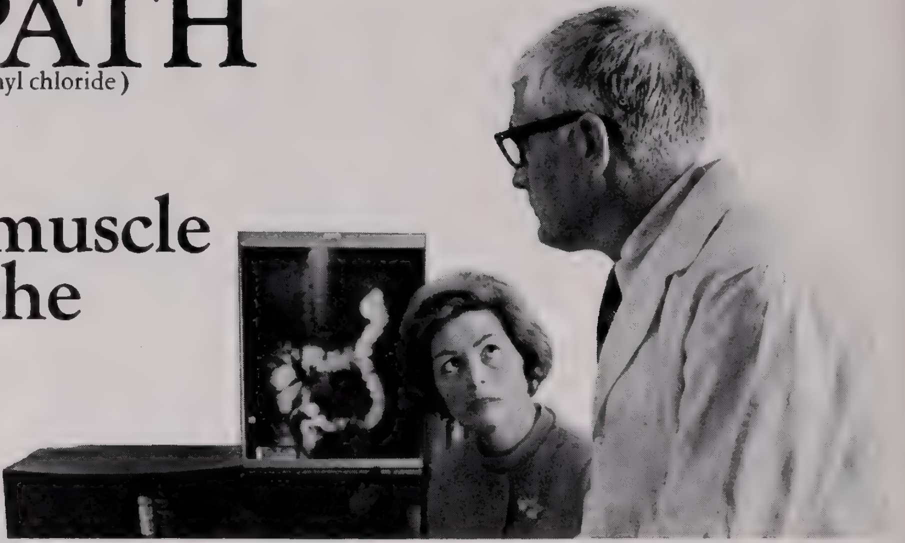

Usual Adult Dosage

One 'Milpath'-400 tablet, three times a day at mealtimes, and two at bedtime. For greater anticholinergic effect, two 'Milpath'-200 tablets, three times a day at mealtimes and two at bedtime. Doses of meprobamate above 2400 mg. daily not recommended.

Indications

Useful in organic and functional disorders with hypersecretion and hypermotility of G.I. tract, especially when accompanied by anxiety, neurosis, or tension states. Should be used as an adjunct to all other therapeutic measures.

Contraindications

Tridihexethyl chloride: Urinary bladder-neck obstructions, e.g., prostatic obstruction due to hypertrophy; pyloric obstructions because of reduced motility and tonus: organic cardiospasm (megaesophagus); glaucoma; possibly in stenosing gastric or duodenal ulcers with significant gastric retention.

Meprobamate: Previous allergic or idiosyncratic reactions to meprobamate.

Precautions

Tridihexethyl chloride: Use cautiously in elderly males (possible prostatic hypertrophy).

Meprobamate: Carefully supervise dose and amounts prescribed. Consider possible dependence or habituation (reported occasionally after excessive use), particularly in severe psychoneurotics, alcoholics, ex-addicts. Withdraw gradually (one or two weeks) after excessive dosage for weeks or months to avoid recurrence of pre-existing symptoms (e.g., anxiety, anorexia, insomnia) or withdrawal reactions (e.g., vomiting, ataxia, tremors, muscle twitching; rarely, epileptiform seizures, more likely in those with CNS damage or latent convulsive disorders). If drowsiness or visual disturbance occurs, reduce dose and advise against activity requiring alertness (driving, machinery operation). Effects of excess alcohol may be increased. Grand mal seizures possible in persons with both petit and grand mal. Prescribe cautiously in small amounts to patients with suicidal tendencies. Prescribe with caution to patients with known sensitivity to compounds of similar chemical structure, e.g., carisoprodol.

Side Effects

The following side effects of components may occur with 'Milpath'.

Tridihexethyl chloride: Severe effects rare on recommended dosage. Anticholinergic effects: dry mouth (fairly frequent at oral doses of 100 mg.), constipation or "bloated" feeling. Possible: tachycardia, dilation of pupils, increased ocular tension, weakness, nausea, vomiting, headache, drowsiness, urinary hesitancy or retention, dizziness.

Meprobamate: Drowsiness, sometimes with ataxia, usually controlled by decreasing dosage, occasionally with aid of central stimulants (e.g., amphetamine). Rarely, allergic or idiosyncratic reactions (usually after one to four doses); in mild form: itchy, urticarial or erythematous, maculopapular rash, generalized or confined to groin. Acute nonthrombocytopenic purpura with cutaneous petechiae, ecchymoses, peripheral edema and fever, transient leukopenia, and one fatal bullous dermatitis (after meprobamate and prednisolone) reported. More severe, very rare hypersensitivity: fever, chills, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (one fatal), anuria, anaphylaxis, stomatitis and proctitis. Treat symptomatically (e.g., epinephrine, antihistamines, possibly hydrocortisone); stop and do not restart the drug. Isolated agranulocytosis, thrombocytopenic purpura, one fatal aplastic anemia reported, but only in presence of known toxic drugs, porphyric symptoms reported but relationship not established. Fast EEG activity, usually after excessive dosage. Impairment of visual accommodation reported by one observer. Fixed drug eruption with meprobamate and cross reaction to carisoprodol reported.

Suicidal attempts may produce drowsiness, lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse, and death. Excessive dosage has led rapidly to sleep, then reduction of vital signs to basal levels. Empty stomach, and if respiration becomes very shallow and slow, cautiously give CNS stimulants (e.g., caffeine, pentylenetetrazol, amphetamine); also pressor amines if indicated.

Supplied

In two strengths:

'Milpath'-400: Yellow, scored tablets.

'Milpath'-200: Yellow, coated tablets.

Before prescribing, consult package circular.

References

1. Harrison, T. R., et al.: Principles of Internal Medicine, Fifth Edition, New York, The Blakiston Division, McGraw-Hill Book Company, 1966, p. 1019. 2. Bockus, H. L.: Gastroenterology, Second Edition, Philadelphia & London, W. B. Saunders Company, 1964, Vol. II, p. 729 et seq.

(1928A01J)

A Practical, Palatable Way of Eating[*]

ANCEL KEYS, Ph.D.[†]
Minneapolis, Minnesota

ANY DISCUSSION of efforts to prevent coronary heart disease must consider dietary management because there is so much reason to suspect that the current ordinary American diet contributes substantially to the development of atherosclerosis and its complications, notably coronary heart disease. This idea is hotly debated by representatives of certain food industries and there is as yet no guarantee that changing the diet in middle-age or older will reduce the likelihood of future heart attacks. Nevertheless, control of the diet can lower the serum cholesterol concentration; and a great many Americans, including physicians, are interested in a practical, palatable diet that will lower the cholesterol level and, perhaps, diminish the risk of future heart attacks. From the response to invitations to take part in the National Diet-Heart Study it can be estimated that something like 10 per cent of the middle-aged population in U.S. metropolitan areas are sufficiently interested to volunteer for dietary trials that would involve much inconvenience and no promise of any real benefit.[1]

Incidence of Coronary Heart Disease

Table 1 summarizes the overall average experience of prospective studies on men in Framingham (Massachusetts), Albany (New York), and Minneapolis-St. Paul (Minnesota). For middle-aged American men, apparently healthy at the entry examination, the risk of developing coronary heart disease within a few years rises steeply with increasing serum cholesterol concentration. If the relative incidence rate for men with entry cholesterol values under 200 is taken as 100, the rate for men with values of 250 is about 285, almost three times greater. The relative incidence rate for men otherwise comparable rises as about the cube, the third power, of the serum cholesterol value and there is no break or "critical level." In regard to serum cholesterol concentration: the lower the better.[2]

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[*] Presented at the Minnesota Symposium on Prevention in Cardiology, May 2-3, 1968 in Rochester, Minnesota.

[†] Professor and Director Laboratory of Physiological Hygiene, University of Minnesota.

TABLE I

Relative incidence rate of coronary heart disease of U.S. white men classified by entry level of serum cholesterol. Average of data on men in Framingham, Mass. (courtesy of Dr. W. B. Kannel), men in Albany, N. Y. (courtesy of Dr. J. T. Doyle) and men in Minneapolis-St. Paul (Keys et al. 1963 Circulation *28*, 381). The age- and area-specific rate for all men regardless of cholesterol level is taken as 100.

Chol., mg/dl	Under 200	200-219	220-239	240-259	260+
Coronary heart disease incidence	47	60	93	134	202

Since no penalty from other disease or other disadvantage is associated with cholesterol levels lower than the current average in the United States, the inference is that a large fraction of the whole American population should be candidates for serum cholesterol control if safe and otherwise acceptable means are available. Roughly, it may be estimated that for Americans aged 40 or more the general average serum cholesterol value is between 230 and 240. Such values may be considered "normal" according to some definitions, but among middle-aged men those "normal" values are associated with about twice the coronary death rate associated with serum cholesterol values 15 per cent lower. Since something like one third of middle-aged white Americans have serum cholesterol values over 240, it could be suggested that a third of our adult population would benefit from serum cholesterol control. Or perhaps the specification should be for the adult population up to age 65 or so, because the influence of serum cholesterol as a risk factor diminishes with age and may be trivial in the sixties and beyond.

Approaches To Cholesterol Control

Effect of Duration & Concentration

All students of the cholesterol-atherosclerosis question agree that whatever may be the action of cholesterol in the blood plasma, the net result must be a function of concentration times the duration of that concentration. Not only is that conclusion consistent with the evidence that cholesterol control that begins only late in life must have less value than lifelong control; it also indicates that short-period reductions of serum cholesterol level are of little or no use. So whatever method is proposed for serum cholesterol, it can have little value if it operates only temporarily.

Surgical Approach

The surgical approach involves shortening the length of the small intestine; the serum cholesterol then falls promptly and stays reduced when operation is done properly. This drastic intervention may be justifiable for some rare individuals but obviously cannot be seriously considered for large-scale application. The drug approach is less readily dismissed.

Drugs

Several drugs—atromid S ("CPIB"), nicotinic acid, thyroid, sex hormones and some resins that sequester cholesterol or bile salts in the intestine—will lower serum cholesterol in almost all people when given in suitable doses. Neomycin taken orally has some cholesterol-lowering effect. With the exception of atromid S, all of the effective preparations have some unpleasant or worrisome side effects; even atromid S may not be devoid of other actions, as was originally claimed. But granting that the side effects of one or more of these drugs are tolerable to many people and true toxicity is not obviously a serious problem, it scarcely seems reasonable to propose that a large proportion of the whole population be dosed with drugs daily throughout life. And yet without continuous and indefinitely prolonged use there can be little prospect of even potential preventive benefit. Conceivably, lifelong drug dosage may have a place for use with some patients but not for the general public.

Diet

Exactly the same stipulation holds for dietary management. No endorsement can be given to short dietary trials, even if the diet does have some temporary effect. To be truly effective, dietary management must aim at establishing a suitable dietary way of life. But this stipulation is not a cause for concern in the case of the diet. The habitual dietary practices of millions of people over many generations can be described as a "suitable dietary way of life" in this respect. Our own prolonged studies on such populations in Greece, parts of

Yugoslavia and parts of Italy indicate no health hazards of any kind from lifelong subsistence on suitably chosen diets that maintain the serum cholesterol level 15 to 25 per cent lower than the U.S. average.

Serum Cholesterol Changes From Known Dietary Changes

Influence of Polyunsaturated Fatty Acids

The average effect of the diet on the serum cholesterol concentration of American men is known from many controlled experiments, especially in mental hospitals and in prisons where metabolic ward conditions can be maintained for prolonged periods.[3-6] Table 2 considers the effect of differences in the percentage of total calories provided by saturated and by polyunsaturated fatty acids in the diet. Monounsaturated fatty acids in the diet, notably oleic acid, have no effect on serum cholesterol concentration when they are exchanged for equal calories of starch in the diet. Briefly, as Table 2 indicates, saturated fatty acids in the diet raise the serum cholesterol level while polyunsaturated fatty acids have an opposite but weaker effect; roughly two grams of linoleic acid would be needed to balance the effect of one gram of palmitic acid. To counter the effect of an ounce of butterfat in the diet it would be necessary to add about two ounces of corn oil to the diet which, of course, poses a problem of total calories and obesity.

TABLE 2

Average change of serum cholesterol (CHOL, mg/dl) in response to changed percentage of dietary calories from saturated (S) and poly-unsaturated (P) fatty acids:

$CHOL_2\text{-}CHO_1 = 2.7\ (S_2\text{-}S_1) - 1.3\ (P_2\text{-}P_1)$

DIET	S	P	CHOL
1) U.S. average	17	5	230
2) A recommended type	8	10	199
3) 2) - 1)	–9	5	–31

Actually, it is an over-simplification to consider all saturated fatty acids as equivalent. The shorter-chain saturated fatty acids, those with fewer than 12 carbon atoms in the chain, have no more effect than equal calories of starch in the diet. The same is true of the 18-carbon saturate, stearic acid, and probably of saturated acids with more than 18 carbons in the chain. In other words, the cholesterol-raising effect of saturated fatty acids is practically restricted to those with 12 to 17 carbon atoms. Accordingly, the chief dietary "enemies" are lauric* (12C), myristic (14C) and palmitic (16C) acids. The recent discovery of the lack of serum cholesterol effect of stearic acid does not do much to alter the calculation for predicted effects of most ordinary diets, but it does mean that chocolate is no longer on the forbidden list of the cholesterol-watcher. The fat in cocoa and chocolate is highly saturated; but stearic acid makes up the great bulk of the saturates, and trials with large quantities of cocoa butter in the diet show no cholesterol-promoting effect.[7,8]

Exogenous Cholesterol Influence

Besides fatty acids, it is necessary to consider exogenous cholesterol supplied in the diet. Again, many controlled experiments on men in prisons and hospitals have shown the effect on serum cholesterol of changes in the dietary cholesterol, all other factors being equal.[5,9] If the dietary cholesterol is expressed in mg. per 1000 calories, its average effect on the serum level is proportional to the square root of that dietary cholesterol concentration, as shown in Table 3. On a diet similar to the U.S. average in regard to fats and cholesterol, the average for middle-aged men is a serum value of about 230, as noted above. If all the cholesterol in the diet could be removed but the diet left otherwise unaltered, the average serum level would be about 207; that is to say, the concentration would fall about 10 per cent. But zero-cholesterol diets are impossible to provide for free-living people. A practical diet sharply restricted in cholesterol still contains something like 100 mg. of cholesterol per 1,000 calories. Change from an ordinary U.S. diet to a diet so low in cholesterol but otherwise unchanged produces an average fall of only about 3 to 4 per cent in the serum concentration. Conversely, the addition of two egg yolks to the daily diet of the average middle-aged man, which would mean an addition of about 200 mg. of cholesterol per 1000 calories, to make a total of about 425 mg/1000 calories, does not have a large effect. On the average that dietary change causes a rise of less than three per cent in the serum cholesterol. The upshot is that dietary cholesterol has some effect in man, but the effect of cholesterol restriction in practical diets is very limited.

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*See Test Your Word Score Page 1213.

TABLE 3

Let Z^2 = dietary cholesterol, mg per 1000 calories, and CHOL = serum cholesterol, mg/dl. Then the change from diet 1 to diet 2 produces the average serum response: $CHOL_2 - CHOL_1 = 1.5\ (Z_2-Z_1)$

ITEM	Z^2	Z	CHOL
1) A common U.S. diet	225	15	230
2) A low-cholesterol diet	100	10	222
3) Zero-cholesterol "	0	0	207
4) A high-cholesterol " (extra 2 eggs/day)	425	21	236

Individual "Cholesterolstat" Setting

The average effects of diets indicated in Tables 2 and 3 relate to average men. But individuals differ intrinsically in their cholesterol metabolism; their "cholesterolstats" have different settings, so to speak. With few exceptions, the higher the intrinsic level of the individual, the more sensitive is the serum cholesterol concentration to the diet and, apparently, also to drugs. In general, persons with very high serum values on an ordinary U.S. diet will show much bigger responses to dietary change than indicated in Tables 2 and 3.

Besides dietary fats and cholesterol, some other dietary items should be considered. Variations in proteins, vitamins and minerals over the range of practical and generally acceptable diets have no significant effects, nor is there any alteration in the serum level when tolerable exchanges are made among sugars and starches. But some complex carbohydrates—pectin and some mucilaginous gums—have a modest cholesterol-lowering effect when they are added to the diet.[10,11] A specific cholesterol-lowering effect of beans and other leguminous seeds in the diet is probably also due to complex carbohydrates.[12]

Practicalities

The first requirement in translating the results from experiments into menus and recipes is to ensure safety. We must be absolutely sure that new diets to be recommended for possible coronary prevention carry no possibility of producing nutritional deficiencies or other dangerous or merely unpleasant physiological or metabolic states. With insistence on a mixed diet of a wide variety of natural foods and recommendation for abundant use of skim milk, leafy and colored vegetables, and fruits, no question of medical acceptability and safety can arise.

Reduce Saturated Fatty Acids

The first requirement for the cholesterol-lowering diet is a sharp reduction in the saturated fatty acids or, to be more specific, lauric, myristic and palmitic acids. In practical terms this means the elimination, or at least severe restriction, of fatty meats, butter, cream, ordinary ice cream, whole milk, lard and highly hydrogenated shortenings, and many commercial pastries. Suitable vegetable oils—corn, sunflower, cottonseed, soybean, safflower, according to preference and availability—should be used for salads and all cooking. Olive oil, though not high in linoleic acid, is low in saturates and is not forbidden for those who like the flavor.

"Fatty meats" include most pork and most of the "better" (i.e., more expensive) grades of beef currently sold in the United States. However, the watchful shopper can find truly lean beef and pork today; the meat industry is responding to the demand of the times. But even apparently lean beef and pork often prove to contain so much saturated fatty acid that small portions, or substitution of other main-dish foodstuffs, are advisable. Substitution is easy. Chicken and turkey are cheap and much more suitable for the cholesterol-watcher. Fish is not so cheap but it is even more suitable than fowl.

There is much misunderstanding about shellfish. Oysters, lobsters, etc., though very low in saturated fatty acids, worry some people because they may be rather high in exogenous cholesterol. But, as noted above, unless the diet can be reduced to nearly zero cholesterol, the effect on serum cholesterol of moderate variations in the dietary cholesterol intake is very small. The ordinary cholesterol-watcher is not forbidden to have a few whole eggs a week, and there is even less to be concerned about in the consumption of shellfish several times a week.

An abundance of fruits and leafy vegetables and generous use of beans, peas, and their relatives as meat substitutes will also help keep the serum cholesterol down. All of the foregoing points are elaborated in detail, with numerous recipes, menus and cooking hints, in a number of books suitable for the general public.[13-19] The net result is that with the help of such books and a little experience the cholesterol-watcher can have unlimited gustatory pleasure with little effort and an actual saving of money.

*Calories**

The substitution of polyunsaturated for saturated fatty acids in the diet is useful, but there has been too much propaganda about the virtue of certain vegetable oils than is warranted by the facts. Simply *adding* corn or other oil to the diet makes no sense; calorie excess raises the serum cholesterol level as well as promotes obesity. No epidemiological evidence can be offered to support the idea of "dosing" with one or another oil. The ordinary current U.S. diet provides some 4 to 7 per cent of total calories from linoleic and other polyunsaturated fatty acids. Natural populations have not been found anywhere who have appreciably higher intakes of the polyunsaturated fatty acids. In our own worldwide studies we find no lack of examples of populations whose serum cholesterol levels and frequencies of coronary heart disease are admirably low compared to the situation in the United States. Not one of those populations has a higher intake of polyunsaturated fatty acids than the ordinary U.S. diet; but the intake of saturated fatty acids is invariably low.

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*See Test Your Word Score Page 1213.

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Barometric Pressure and Disease

South winds induce dullness of hearing, dimness of visions, heaviness of the head, torpor, and languor; when these prevail, such symptoms occur in diseases. But if the north wind prevail, coughs, affections of the throat, hardness of the bowels, dysuria attended with rigors, and pains of the sides and breast occur. When this wind prevails, all such symptoms may be expected in diseases.*

***Hippocrates.**

Edward N. Peterson, M.D.

The cover photo was taken in an alpine meadow on the west side of Mt. Ranier in Washington and it is particularly beautiful when the mountain flowers are in bloom in August.

Doctor Peterson spent eight years in Oregon; four and one-half in private practice and three and one-half in academic medicine on the full-time faculty of the University of Oregon Medical School. An outstanding professional opportunity was offered to him in the Department of Obstetrics and Gynecology at the University of Pittsburgh School of Medicine in July, 1968. His subspecialty is cardiovascular physiology of pregnancy and his main research interest is in maternal blood flow changes as related to reproductive failure in women.

While living in the West he and his family developed the hobby of camping in the primitive areas of the Cascade Range. The children by 1967 had matured enough to go on backpacking trips and it was then they chose to hike the trails on Mt. Ranier.

During one of these hiking trips that summer Dr. Peterson noticed the pink glow and reflection on his way to a spring for water and immediately ran back for the camera. *Seconds* afterward the picture was taken the color had faded and the mountain was dark.

Dr. Peterson grew up in Virginia, Minnesota, where his father is a practicing general surgeon. His guidance and example led Dr. Peterson and his brother, Dr. Charles A. Peterson of Minneapolis to attend the University of Minnesota Medical School from which Dr. Ed. Peterson was graduated in 1954.

He and his family now live in suburban Pittsburgh in an area called Fox Chapel. All four children attend public school and their mother, freed of daily homemaking responsibilities, has also returned to school. Mrs. Peterson graduated from the University of Minnesota School of Nursing in 1953 and is now completing studies in the University of Pittsburgh Graduate School of Public Health, working for a master's degree in Maternal and Child Health.

School of Salernum

For Oyntment iuyce of Onyons is assigned,
To heads whose hair fals faster than it growes:
If Onyons cannot helpe in such mishap,
A man must get him a Gregorian cap.*

—**Regimen Sanitatis Salerni**

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*A wig of a style designed by a barber named Gregory.

Editor's note: Succinct and impish advice to the bald: if a scalp tonic of onion juice fails to grow hair, a wig is the only alternative and the last resort. It seems that in ten centuries Medicine has not been able to improve on onion juice as a trichotropic agent.

Overweight and Obesity*

The Associated Cardiovascular Risk

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Boston, Massachusetts

THE TERMS OVERWEIGHT and obesity are not necessarily synonymous.

Overweight refers to body weight in excess of a standard, whether the standard be average, ideal, or desirable weight, but it may bear little relation to the person's fat status. *Obesity*, on the other hand, refers to the condition of fatness or to an excess amount of adipose tissue. Excess weight over a standard does not tell us whether it represents fat, bone, muscle, fluid, or the relative contributions of these components. What part of the weight can be charged to the fatty component? And since there is no universal agreement on the degree of overweight which constitutes a presumption of obesity, some consider a deviation of even 10% above average or desirable weight as constituting such a presumption; others use 15% or 20% as the outside of normality, and still others use an even higher percentage. Accordingly, not all overweight persons are obese, and conversely some persons can be obese without being markedly overweight. It depends on the amount of overweight and the base line of the abstract value, and whether the overweight is in reality fat.

Height-Weight Tables

The value of the height-weight tables popularized by life insurance companies is subject to severe limitations;[1,2] the derivation of the degree of obesity from these tables can be quite misleading. This is particularly true in the case of the overweight designations based on the "desirable" weight tables of the Metropolitan Life Insurance Company, since these arbitrary tables give weights for height far below the average weights for height of the general population. If degree of fatness is sought, then the criteria of obesity should be based on actual

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*Presented at the Minnesota Symposium on Prevention in Cardiology, May 2-3, 1968 in Rochester, Minnesota.

†Senior Research Associate, Biological Anthropology, Harvard University, School of Public Health, Department of Nutrition.

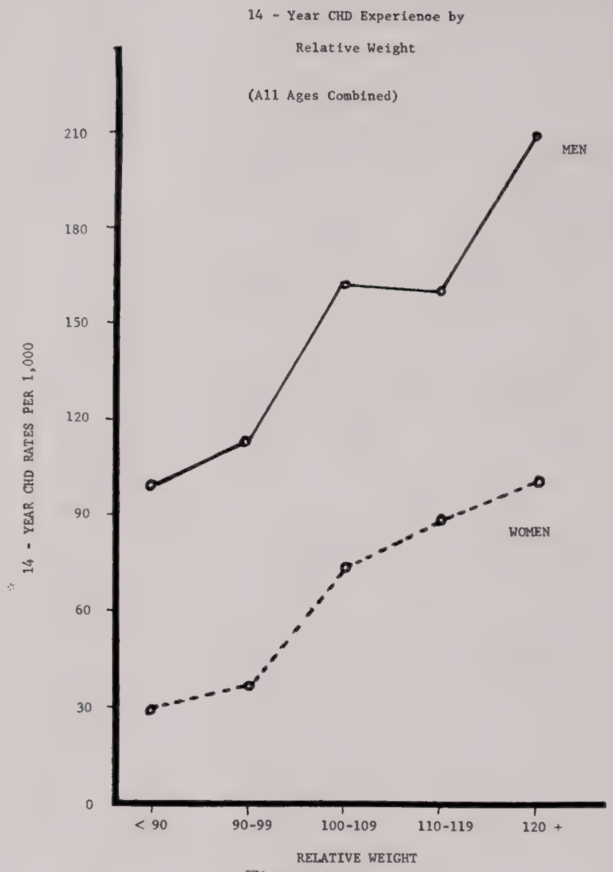

Figure 1

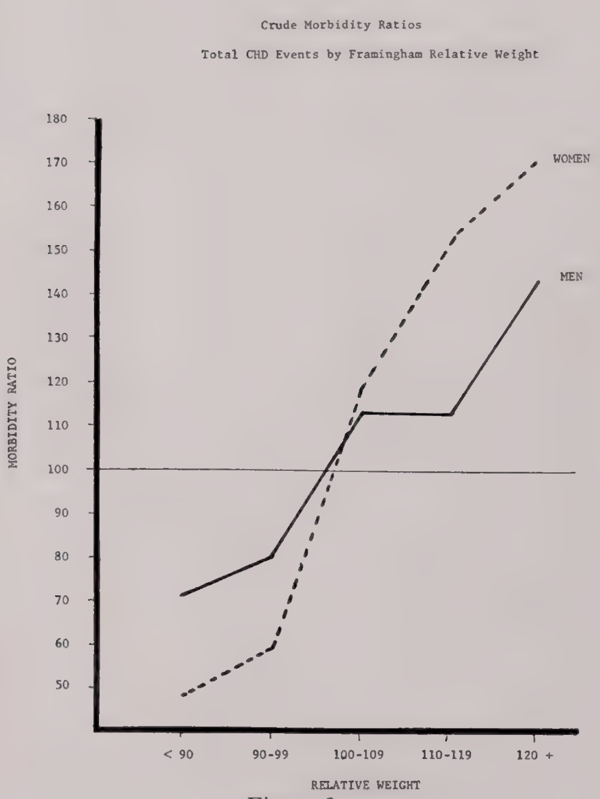

Figure 2

measurement of fatness and not on inference of fatness.

Skinfold Measurements

The appearance of the naked patient is the usual basis for the diagnosis of obesity by the experienced clinician and, as a qualitative guide, is usually reliable. But when a quantitative estimate is desired, skinfold measurement is recommended. For the clinic and for large-scale surveys, it has been shown that skinfold measurements, particularly those of the triceps and subscapular skinfolds, are relatively simple and practical measures of adiposity.[3]

Fatness and Cardiovascular Disease

To define overweight and obesity is important for several reasons. First, by far the largest amount of information bearing on the relationship between obesity and cardiovascular disease is based on overweight designations. It is only over the last decade or so that data have been collected on the relationship between direct measurement of fatness and cardiovascular disease, through the use of skinfold values. Secondly, in these studies, there is no uniformity in the degree of overweight designations or in the base line from which the overweight percentages have been computed. They vary from 10% up to even 30% relative weights. Thirdly, even when skinfold measurements are used, such measurements have not been taken in the context of body build types. Accordingly, even while there is at present a wealth of information bearing on "fatness" and cardiovascular disease, we do not know for sure what part of the effect observed is the result of fatness or of body build type. Thus, we do not know whether a moderate amount of adipose tissue in a dominant ectomorph (linear, attenuated body build type) is as deleterious or lethal a factor as a considerably greater quantity of fat in a dominant mesomorph (heavily boned and muscled in individual) or a still greater excess in a dominant endomorph.

Mortality

Insurance company studies indicate that overweight is associated with increased mortality, particularly from cardiovascular diseases. The monumental study of the Society of Actuaries pertaining to build and blood pressure found progressively higher mortality rates from coronary heart disease with increasing degrees of overweight.[4] Dublin and Marks of the Metropolitan Life Insurance Company show statistically that overweight persons who reduce and stay reduced may substantially increase their life expectancy.[5]

Clinical studies, however, have produced conflicting reports on the role of overweight or obesity in coronary heart disease.[6,7,8,9,13] In some instances, only extreme obesity was associated with an increased rate of development of coronary heart disease, though most epidemiological studies show a relationship between overweight or obesity and the morbidity and mortality from coronary heart disease.[10,11,12]

Cholesterol and Hypertension

Keys and Stamler found that overweight or body fatness did not appear to be an important risk factor *except* insofar as these conditions were related to high serum cholesterol or to hypertension, hyperlipidemia, and diabetes mellitus, except when obesity is very gross.[14]

Conflicting Findings

These conflicting results may be due to a lack of consistency in the criteria of overweight or obesity, to differences in the nature of the populations studied, such as geography, diet, physical activity, body build, habits, "style of life," or to associated diseases and differential cardiovascular risk factors such as hypertension and hyperlipidemia. These factors must be held constant in the analysis. Among the epidemiological investigations, some are prevalence studies and others are long-term prospective studies giving incidence rates.

We believe, as has been shown by the Framingham Heart Study, that the most important reason for the failure of controlled clinical and epidemiological studies to give consistent results has been the failure of these studies to relate overweight or obesity to each specific overt manifestation of coronary heart disease[10]; conflicting reports have arisen from the differences in the proportion of angina pectoris, sudden death, and myocardial infarction included in the cases reported. For 14

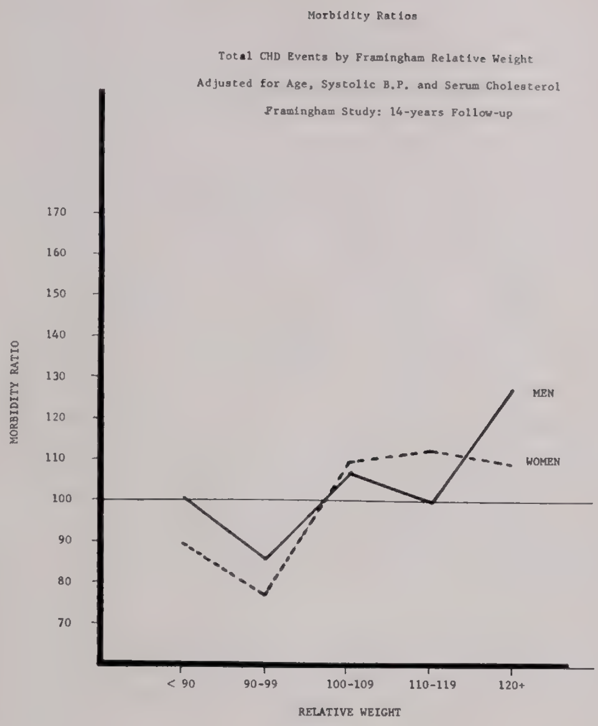

Figure 3

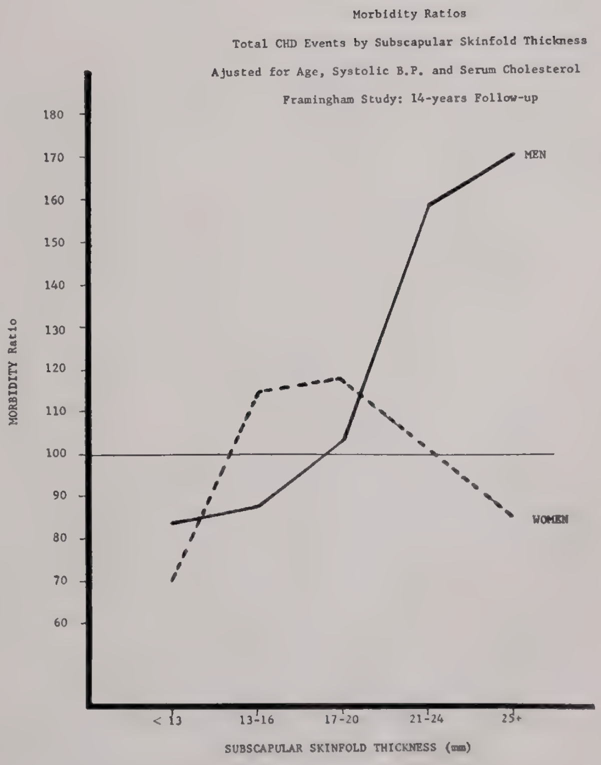

Figure 4

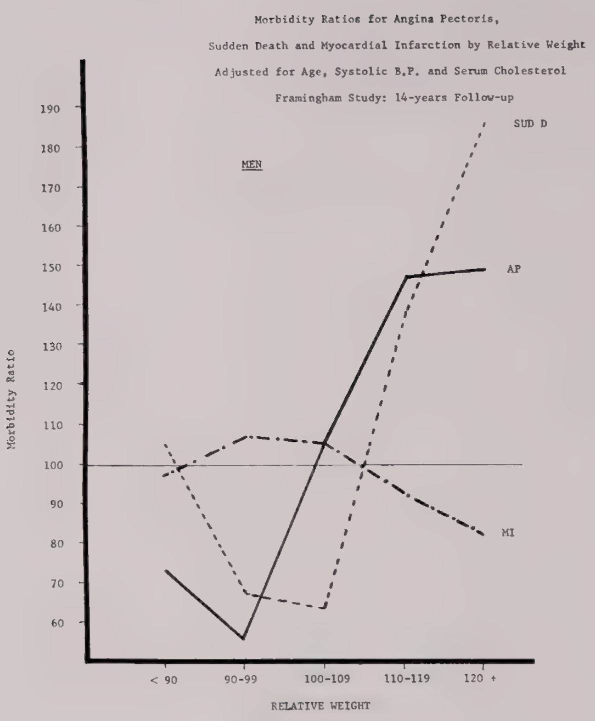

Figure 5

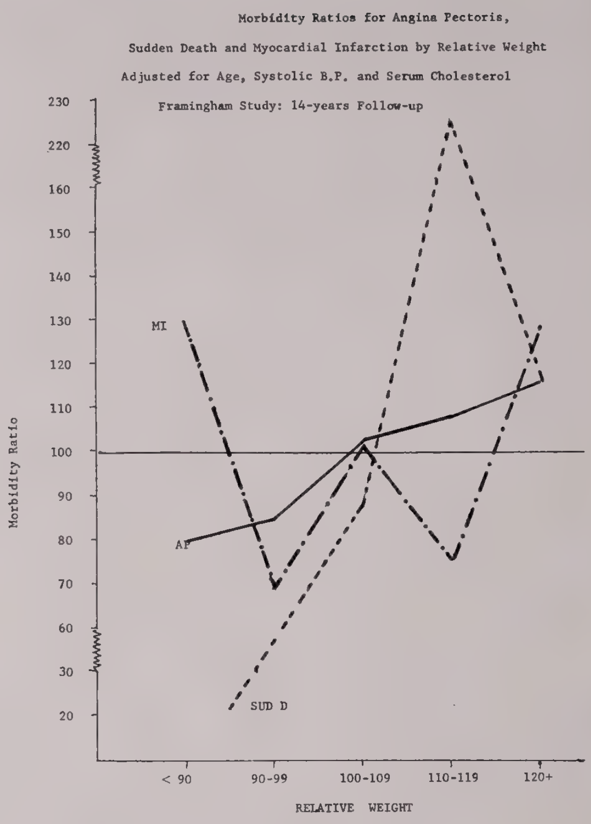

Figure 6

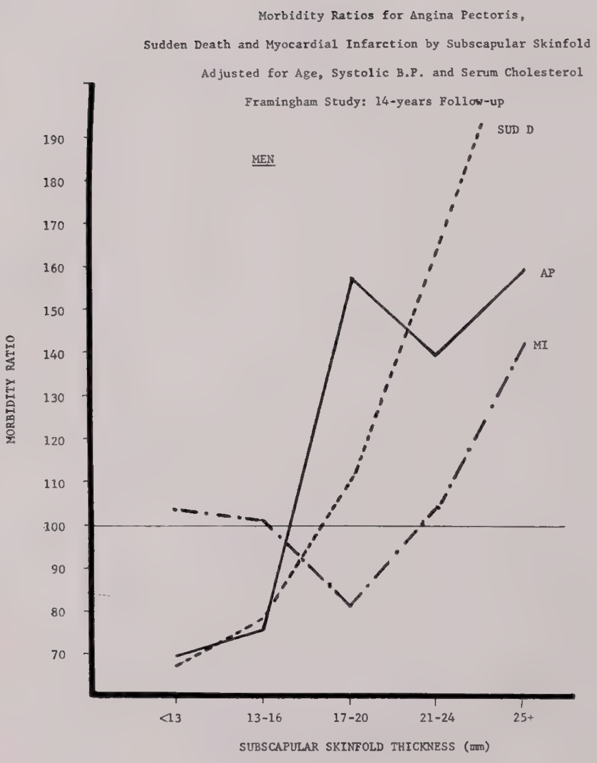

Figure 7

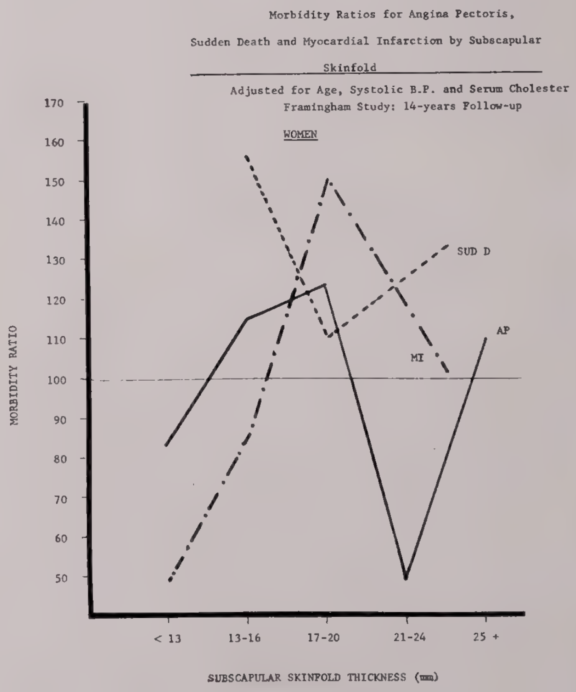

Figure 8

years men and women between the ages of 30 and 62 years have been measured by both relative weight and skinfold thickness. Those taken at the initial examination show that the clinical manifestations of coronary heart disease are roughly proportional to the degree of overweight and adiposity on entry (Figures 1 and 2). However, when total coronary heart disease was broken down into its specific manifestations it was found that, while obesity was clearly related to angina pectoris and sudden death, it was not significantly related to myocardial infarction (Figures 3 to 8), even when adjustments were made for age, hypertension, cholesterol level and diabetes. When these latter factors were present, the effect of adiposity on these coronary heart disease events was more pronounced, though in women there was no independent effect of obesity when adjustments were made for age, hypertension, cholesterol level and diabetes. But when these atherogenic factors are present, obesity in females is related to angina pectoris and sudden death but not to myocardial infarction.

Furthermore, it was noted that while overweight persons tended to develop more hypertension, lipid abnormalities and diabetes—conditions usually associated with an early development of atherosclerosis—autopsy studies on subjects who had participated in the Framingham Study[15] showed no significant correlation of relative weight with the extent of atherosclerotic disease in the coronary circulation (Table 1). Heart weight, however, was clearly related to the degree of adiposity (Table 2).

Conclusions

In summary, the seemingly contradictory findings of insurance, clinical, and epidemiological investigations appear to be explained. Most of them are probably correct in the context given but are not fully explicit and revealing. This is because the results have been almost universally given in terms of the rubric* of total coronary heart disease morbidity or mortality. But when the rubric is broken down into the various manifestations of coronary heart disease such as angina pectoris, sudden death, and myocardial infarction, the inconsistencies become clarified.

Our best present knowledge would indicate that overweight or obesity is a serious cardiovascular health hazard and a potent force for morbidity and mortality from coronary heart disease. In both sexes, the risk of angina pectoris and sudden death appear to be roughly proportional to the degree of obesity, and the very grossly obese have an unusual propensity to sudden unexpected deaths. Obesity, however, does not appear to be a significant factor predisposing to myocardial infarction. In men, the risk of angina pectoris and sudden death is apparently independent of associated atherogenic factors such as hypertension, higher cholestrol levels and diabetes; but when these factors are present the deleterious effect of obesity is considerably increased. In women, however, there is no independent effect of obesity in connection with angina pectoris and sudden death, but there is a strong relationship with obesity when it is present in association with hypertension, higher cholesterol levels and diabetes.

TABLE 1

Evidence of Compromised Circulation
By Relative Weight
(Both Sexes—All Ages)

		Artherosclerotic Coronary Vascular Disease	
Relative Weight	No.	Intima Score Mean	Lumen Score Mean
<90	14	1.8	1.9
90-99	14	1.9	1.7
100-109	19	2.8	2.6
110-119	8	2.6	2.6
120+	20	2.2	2.2
	—		
	75		

TABLE 2

Heart Size
According to Framingham Relative Weight
At Initial Examination
(Both Sexes—All Ages)

Relative Weight	No.	Mean Heart Weight
<90	14	339
90-99	14	449
100-109	19	458
110-119	8	478
120+	20	490
	—	
	75	

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*See Test Your Word Score Page 1213.

It would appear that obesity may act as a precipitating cause in producing angina pectoris and sudden death, possibly owing to the increased work load imposed on the heart. Excess adiposity, on the other hand, does not appear to make a significant contribution to the atherosclerotic process and seems to be relatively independent of myocardial infarction.

With respect to coronary heart disease prevention, avoidance of obesity is indicated because of its association with the development of atherogenic traits such as hypertension, lipid abnormalities and diabetes. Weight reduction in persons with these atherogenic traits improves these factors and probably delays the onset of symptomatic disease. Weight reduction in obese persons improves exercise tolerance and reduces risk of initial or subsequent coronary heart disease events.

My concluding point has to do with body build type considered apart from adiposity. What is interesting in the Framingham data is that, in virtually every single instance, those ectomorph type persons with the lowest relative weight values, those under 100 pounds, showed the lowest risk of total coronary heart disease, angina pectoris, sudden death and myocardial infarction. In addition, they exhibited fewer atherosclerotic processes and smaller heart size. If this is so, then it would appear that ectomorphic physical types are less prone to manifestations of coronary heart disease events of all forms than other body build types. This reinforces our contention that body build types and fatness should be studied conjointly.

Acknowledgment

I wish to express my appreciation to Dr. William B. Kannel, Director of the Framingham Heart Study, for providing me with much of the data presented and for permission for their use.

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Hindsight

Backward, turn backward,
O Time, in your flight—
I've just thought of a comeback
I needed last night.

Maxwell Droke: The Speaker's Handbook of Humor.

Elevated Blood Sugar*

The Associated Cardiovascular Risk

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Ann Arbor, Michigan

THE FREQUENT COEXISTENCE of diabetes and coronary heart disease has been known at least since the early 1920s. In 1941 Woodyatt stated that it is the *mild* form of diabetes which appears to be particularly associated with coronary disease.[1] The argument may be taken one step further to the proposition that the association is not so much with diabetes but with decreased glucose tolerance, considering glucose tolerance as a continuous variable, like blood pressure or the serum cholesterol level.

Abnormal Glucose Tolerance

Data from clinical studies based on oral glucose tolerance tests, as summarized by Wahlberg,[2] indicate that the proportion of patients with coronary disease who have abnormal tests differs from study to study being 61 per cent on an average. The frequency of abnormal results is much higher than one would expect in the general population.

Gorlin and his group in Boston have demonstrated latent diabetes in a large proportion of patients with coronary disease as demonstrated by cinearteriography.[3] The results of a similar study[4] in 27 patients with abnormal coronary arteriograms disclosed eighteen with abnormal glucose or cortisone-glucose tolerance tests, and the majority of these patients showed multiple metabolic abnormalities. Of the seven patients who had three abnormalities, three were classified as Type IV and the remainder as Type II by the lipoprotein nomenclature of Fredrickson. Hatch and co-workers found abnormal glucose or cortisone-glucose tolerance tests among young men with coronary heart disease[5] 6.7 times more often than expected. Tzagournis and associates[6] similarly demonstrated abnormal glucose tolerance in patients with coronary disease and reported that this phenomenon was accompanied by an increase in immuno-reactive insulin levels.

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*Presented at the Minnesota Symposium on Prevention in Cardiology, May 2-3, 1968 in Rochester, Minnesota.

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Results from several[7,8,9,10,11] epidemiological investigations strongly support these clinical observations.

This array of evidence makes a strong case for regarding elevated blood sugar as a risk factor in the development of coronary heart disease, even though most of the evidence is not based on prospective observations. The question, therefore, arises whether glucose tolerance is correlated with any of the other established or suspected risk factors.

Elevated Blood Pressure

The only other risk factor for which there is definite evidence of a strong association with glucose tolerance is blood pressure. Clinically, the association between hypertension and diabetes has been recognized for a long time. Indeed, Pell and d'Alonzo,[12] and Stamler[13] report that the association between diabetes and coronary disease has no direct significance since non-hypertensive diabetics showed no increased risk. In the Tecumseh Study hypertension and hyperglycemia are also associated, but the coexistence does not account for the relationship between hyperglycemia and coronary disease.[7] More recently, however, Conn[14] has suggested that primary aldosteronism might be a common denominator.

Serum Lipids

There is no correlation between serum cholesterol and blood sugar levels in data from the Tecumseh population.[15] With regard to triglycerides, the data in the literature are not consistent. Most data, including those of Albrink, indicate only a modest association between hyperglycemia and hypertriglyceridemia as reviewed elsewhere.[16] In a small sample of 74 persons in Tecumseh, there was a tendency for persons with a high level of one to also have a high level of the other.[17] In the Pensacola 1000 aviator study,[18] there was likewise an association between triglyceride levels and glucose tolerance. One might have anticipated that patients with marked degrees of carbohydrate-sensitive hypertriglyceridemia would show reduced glucose tolerance,[16] but this was not so either in Ahrens' original series[19] or in the subsequent data by Kuo and Bassett.[20]

Weight Factor

The data from Tecumseh show no association between relative weight and glucose tolerance.[15] The actual relationship might be with weight *gain* rather than weight itself. Whatever the true connection between hyperglycemia and overweight, the association does not appear to be strong, notwithstanding the fact that weight reduction improves glucose tolerance. One tends to think of elevated blood sugar, triglycerides and weight as a triad, but Bierman[21] believes that these three abnormalities are basically different conditions which, being quite common, frequently happen to co-exist. Obesity, moreover, may not be a single entity. For instance, in the Tecumseh data, Evans and Ostrander[22] found that the sum of the subscapular and triceps skinfolds did not correlate with triglycerides; but their ratio, which is a measure of peripheral as opposed to central obesity, did so very significantly. Glucose tolerance correlated with neither skinfolds nor their ratio.

Multiple Variables

In these complex metabolic interrelationships, it may be a mistake to look only at two variables at a time. There may be a clustering of these abnormalities in some people but not in others, and such clustering may be masked in bivariant* analyses. We should search for syndromes of metabolic patterns of common disorders in the general population which, after all, generates the multitude of persons who develop coronary heart disease.

There is no evidence from the Tecumseh Study data that glucose tolerance correlates with other risk factors such as smoking[23] or physical inactivity.[24] Thus, if glucose tolerance is a risk factor toward coronary disease, it is likely to be a risk factor in its own right, although its association with high blood pressure may mediate part of this effect. There is a great need to find out more about the interrelationships between glucose tolerance, triglycerides and the lipoprotein pattern characterized in its fully expressed form by Fredrickson's type IV. Such data will be an essential part of determining the role of glucose tolerance and triglyceride levels as a risk factor.

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*See Test Your Word Score Page 1213.

Atherogenesis*

Assuming the existence of a causal relationship between hyperglycemia and coronary heart disease, what are the possible mechanisms of atherogenesis? What facet of glucose intolerance might increase thrombotic tendency or myocardial susceptibility to infarction in a heart with an already marginal blood supply?[16]

Insulin Excess

The few animal experiments reported provide little help,[16] since alloxan-induced diabetes protects against atherosclerosis in rabbits, while, contrariwise, insulin prevents regression of atheromata in cockerels and also depresses lipase activity in aortas of alloxan-diabetic rats. That elevated insulin levels may be detrimental is suggested by a few studies in which immunoreactive insulin was shown to be elevated in patients with coronary disease, most recently by Tzagournis and coworkers.[6] and in at least three similar, limited studies previously reviewed.[16] It seems that insulin is involved specifically, because insulin-like activity was not found to be elevated in persons with coronary heart disease in the Tecumseh study.[17] According to Vallance-Owen,[25] on the other hand, the factor involved is the insulin antagonist which he has described. Delayed but enhanced insulin output is, of course, part of the abnormal response to a glucose load. It is true that in early or latent diabetes the output of insulin per unit of blood-sugar rise is less than normal. However, the total, as opposed to the relative, release of insulin is higher than normal. This absolute rather than relative insulin level is, perhaps, the signal which determines the effect of insulin on arterial lipids.[16]

Insulin Deficit

On the basis of the data just cited, it is plausible that coronary disease and hyperglycemia are linked because the metabolic defect manifested as hyperglycemia is accompanied by hyperinsulinemia which enhances atheroma formation. It seems hard to reconcile this attractive hypothesis with the equally attractive view of Kendall, in a recent editorial in *Circulation,* that the fault lies with insulin lack rather than insulin excess.[26] He recalls that the arterial intima is essentially avascular and hypoxic and that the integrity of the arterial cells depends on the energy supplied through anaerobic glycolysis. Insulin lack prevents glucose utilization as a source of energy and leads to arterial damage. This damage, which would be the initial pathological change, makes the artery susceptible to lipid infiltration. Insulin lack over large parts of the day may result from our habit of taking infrequent meals high in fat and low in slowly absorbed complex carbohydrates. By contrast, a constant supply of blood glucose, maintained by frequently ingested and slowly released complex carbohydrates, would assure a constant, adequate level of insulin. Large, widely-spaced meals high in simple carbohydrates cause both an irregular supply of insulin and a dissociation in the absorption of carbohydrate and fat.

When fat absorption is rising, carbohydrate absorption and insulin release are past their peak, and adipose tissue cells are filled with fat newly synthesized from the glucose just absorbed so that more of the absorbed fat is channelled to the liver to be converted into more lipoprotein which is then deposited in an artery already damaged through insulin lack. Thus, according to Kendall, the vicious circle closes. This theory and the hyperinsulinemia hypothesis are not necessarily mutually exclusive. If low levels of insulin are detrimental to the integrity of arterial cells, excessively high levels may be equally harmful, on account of the lipogenic action of insulin. It may be anticipated that there will be alternative or additional mechanisms proposed to explain the coexistence of hyperglycemia and coronary disease.

Treatment of Abnormal Glucose Tolerance

Is it desirable to treat people who have abnormal but not diabetic glucose tolerance tests? The answer to this question is now known. Drugs which act by releasing insulin may or may not be desirable. Although weight reduction frequently normalizes glucose tolerance, it is unknown what amounts, proportions and kinds of fat and carbohydrate in the diet are most apt to convert an abnormal curve to normal. Frequency of meals may also be a factor. On the basis of the tenuous hypothesis proposed, the criterion of a good dietary regime would not be primarily the normalization of the glucose tolerance test but the achievement of diurnally optimal insulin levels.

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*See Test Your Word Score Page 1213.

Conclusions

There is clearly much room for research. What action should be taken, on the basis of current knowledge, if a person has a marginal abnormality in glucose tolerance? If the finding is clearly isolated, probably nothing; if associated with hypertension or obesity, both should treated; if associated with elevated serum lipids, first attention should be directed toward the lipids. In some instances, these measures will unaccountably rectify hyperglycemia. In others, the physician will have to stand by and practice the difficult art of *masterly* inactivity, which is quite different from *plain* inactivity. The answer whether or not to treat borderline hyperglycemia by diet or hypoglycemic drugs must come from clinical trials, which are now beginning to be instituted. In the meantime, there is a good case for believing that diminished glucose tolerance increases the risk of coronary heart disease and that the mechanism involved holds a major clue to the basic etiology of atherosclerosis.

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16-26. May be secured from the author or the reprints.

A few people die young at 95 or 100. But a larger number become senile wrecks at 21. The growing cult of prolonging life, no matter how parasitic or obstructionist, is terrifying. Too many people are boasting about "hitting 70" or "hitting 80" who never hit anything else in their life, except perhaps a golf ball or a bottle.—Simeon Stylites

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Precautions: Drowsiness, anorexia, slight gastric distress can occur. In excessive drowsiness, consider longer dosage intervals. Persons on full dosage should not operate vehicles. Nonsusceptible organisms may overgrow; treat superinfection appropriately. Treat beta-hemolytic streptococcal infections at least 10 days to help prevent rheumatic fever or acute glomerulonephritis. Tetracycline may form a stable calcium complex in bone-forming tissue and may cause dental staining during tooth development (last half of pregnancy, neonatal period, infancy, early childhood).

Adverse Reactions: *Gastrointestinal*—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. *Skin*—maculopapular and erythematous rashes; exfoliative dermatitis; photosensitivity; onycholysis, nail discoloration. *Kidney*—dose-related rise in BUN. *Hypersensitivity* reactions—urticaria, angioneurotic edema, anaphylaxis. *Intracranial*—bulging fontanels in young infants. *Teeth*—yellow-brown staining; enamel hypoplasia. *Blood*—anemia, thrombocytopenic purpura, neutropenia, eosinophilia. *Liver*—cholestasis at high dosage.

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DOW

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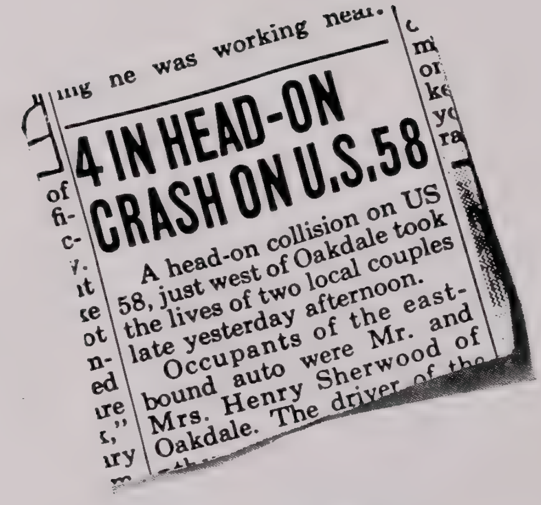

ing he was working near.

4 IN HEAD-ON CRASH ON U.S. 58

A head-on collision on US 58, just west of Oakdale took the lives of two local couples late yesterday afternoon.

Occupants of the east-bound auto were Mr. and Mrs. Henry Sherwood of Oakdale. The driver of the

Hank and Marilyn.

Your best chance to head off a "head-on" is to think negatively. Assume that behind every oncoming truck or car there's a good guy about to make a bad mistake. And, be prepared to get out of his way if he does.

Whenever, wherever you drive . . . drive defensively. Watch out for the other guy. It's the best way there is to watch out for *you*.

Watch out for the Other Guy.

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Obesity and Nutrition Education

Community Approach to Prevention of Coronary Heart Disease*

GEORGE CHRISTAKIS, M.D.†
New York, New York

THE PREVENTION and treatment of obesity as an effective deterrent to the development of coronary heart disease is one of the greatest challenges facing medicine today. No condition, as Dr. Van Itallie observed, is easier to diagnose and more difficult to treat; for the road to weight reduction, as evidenced by the medical literature, is paved with the good intentions of nutritionists and physicians recommending regimens from anorexigenic‡ agents to starvation, and multitudes of reducing diets of various proportions of carbohydrates, fats and proteins. The long-term success of weight reduction regimens remains pitiable.

Indeed obesity *is* a complex problem, a large and elusive shadow, that has followed man throughout the course of history. It is deeply interwoven with his psychic nature and with his culture and environment, and it is now one of the major health problems of western civilization.

Results and Obesity Clinics

Bureau of Nutrition

Community approaches to weight reduction have been relatively few and unsuccessful. The Bureau of Nutrition Obesity Clinic regimen included a 1200-calorie reducing diet. Our review of 2,045 obese subjects treated in these clinics revealed that approximately 26 per cent attained normal weight or within 10 per cent of normal weight, using Metropolitan Life tables as criteria of "normalcy." Seventy-four per cent failed to achieve this.

These results would appear singularly disappointing were it not for the fact that those who failed to attain our strict criteria of normal weight did lose, nevertheless, a considerable amount of weight. However, the complex and tragic aspect of obesity is again in evidence when one considers the percentage of weight loss that is regained.

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*Presented at the Minnesota Symposium on Prevention in Cardiology, May 2-3, 1968 in Rochester, Minnesota.

†Associate Dean and Professor, Community Medicine (Nutrition), Mount Sinai School of Medicine.

‡See Test Your Word Score Page 1213.

Mt. Sinai Hospital Nutrition Clinic

Since January of this year, we have initiated a new weight-reduction program in the Nutrition Clinic of the Mount Sinai Hospital. The screening of obese patients is carefully accomplished by detailed physical examinations: anthropometric measurements of body composition, and laboratory detaminations including a hemogram, serum cholesterol, triglyceride, lipoprotein electrophoresis, phospholipids, and a serum vitamin profile of vitamins A, beta carotene, C and B_{12}. Efforts in small group sessions with experienced nutritionists, using attractive audiovisual techniques, do not appear to be meeting with any greater success than the Bureau of Nutrition program.

Anti-Coronary Club Project

However, the results of the Anti-Coronary Club Study Project now in its eleventh year are most encouraging. The objectives of the Club are the reversal of the risk factors of hypercholesterolemia and obesity.

Detailed dietary history analyses were made of 570 Anti-Coronary Club subjects by age and weight status before they were given a serum-cholesterol lowering diet.

Results of Serum-Cholesterol Lowering Diet

Calorie Intake

In every age group, the excess caloric intake of the overweight men was approximately 200 calories per day compared to the normal-weight men. This relatively moderate excess of calories in the face of the decreasing caloric requirement of advancing age, plus the accompanying sedentariness of urban life very likely play important roles in the pathogenesis of obesity.

Consumption of Fat

Regardless of weight, the subjects consumed less fat with increase in age. In all age groups studied, the obese men ate more fat than normal weight men, though the percentage of fat derived from saturated, monounsaturated and polyunsaturated sources remained quite constant. This is reflected in the similarity of the polyunsaturated to saturated fatty acid ratios in the adipose tissues of both the normal-weight and the obese subjects. This finding resulted from fatty acid composition studies of subcutaneous adipose tissue aspirated from normal weight and obese subjects.

Prevalence of Hypertension

The relative prevalence of hypertension (over 95 mm diastolic) and hypercholesterolemia (over 260 mg%) is given in Table 1.

Incidence of Coronary Events

The Prudent Reducing Diet is summarized in Tables 2 and 3. In Table 1 the effects of the "Regular Prudent Diet" (for normal-weight men) and the Prudent Reducing Diet are seen in reversing obesity, hypercholesterolemia and hypertension. The Anti-Coronary Club data collated as of November 30, 1967, are given in Table 4. We observed 17 confirmed new coronary events in 941 experimen-

TABLE I

Percent of Risk Factors Among 332 Experimental and 329 Control Subjects at Time of Entry and After 2 and 4 Years of Observation

	Experimental			Control		
Risk Factors	Entry	2-year	4-year	Entry	2-year	4-year
None	16.6	61.3	59.0	34.0	35.8	35.3
Hypercholesterolemia*	42.8	20.7	19.9	38.3	30.4	32.2
Obesity†	56.3	15.7	17.8	45.3	45.8	44.1
Hypertension‡	25.9	10.9	9.9	10.9	11.1	13.1
None	16.6	61.3	59.0	34.0	35.8	35.3
Any one	46.4	31.6	34.6	40.4	43.6	43.5
Any two	32.5	5.5	6.0	22.5	18.2	17.9
All three	4.5	1.6	0.3	3.0	2.4	3.3

*Serum cholesterol of 260 mg/100 ml serum or more.

†At least 15% more optimum weight presented in the Metropolitan Life Insurance Company tables of weight for height-build-sex, further modified by subjective evaluation of panel of physicians based on skin-caliper measurements and appearance.

‡Diastolic pressure of 95 mm Hg or more.

tal subjects totaling 3,954 man-years of experience vs. 32 events among 457 control subjects totaling 3,122 man-years of experience. Per 100,000 man-years of experience, the incidence rate of new events for the experimental group is 430 vs. 1,025 for the controls.

Concluding Comments

A two-year study was conducted to identify sociological and psychological attributes of subjects remaining in the study and those who dropped out. By analysis of 370 interviews with persons from both groups, specific behavioral patterns were delineated. Those who dropped out of the study were more closely identified with a 'parochial' orientation. They belonged to a closed, shared and traditional social system. By contrast, members of the study who remained active showed traits of a 'cosmopolitan' orientation. They were open, individual, and progressive. Such information will be useful if methods developed by the Anti-Coronary Club are incorporated into public health programs for the prevention of coronary heart disease.

The unusual degree of success in reducing the weight of obese subjects in this Club, followed by maintenance of normal weight, may be attributable both to the unusual composition of the group and to the intense nutritional guidance given the subjects by the study's public health nutritionists. Subjects are seen at least every six weeks upon entry to the study. During the active phase of weight reduction,

TABLE 2

The Anti-Coronary Club Reducing Diet

	"Prudent Reducing Diet" (1600 Calories)	
Nutrient	g	% Calories
Protein	140	35
Carbohydrate	180	45
Fatty acids	33.5	19
Saturated fatty acids	13.8	7.8
Monounsaturated fatty acids	11.4	6.5
Polyunsaturated fatty acids	8.3	4.7
P/S ratio	0.6	

TABLE 3

The 1600-Calorie Anti-Coronary Club Study Reducing Diet

Breakfast:		Calories
4 oz. citrus fruit or juice or 50 calories from tomato juice, strawberries or lemon in season	50	
1 egg* or 2 oz. cottage cheese	75	
1 slice bread (1 oz.)	75	
Total		200
Lunch or Supper:		
4 oz. fish or seafood† or poultry or lean meat‡	200	
12½ calorie value vegetable (all you want#/)	25	
2 slices bread	150	
1 serving fruit containing 75 calories	75	
Total		450
Dinner:		
8 oz. fish§ or poultry or meat[1]	350	
1 portion 25 calorie value vegetable	25	
12½ calorie value vegetable (all you want/)	25	
1 slice bread	75	
1 serving fruit containing 75 calories	75	
Total		550
Between meals and at bedtime:		
2 glasses skim milk//	170	
3 servings of fruit or fruit juice, 75 calories each	225	
Total		395
Grand Total		1595

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* No more than four eggs per week.

† At least three lunches (preferably more) per week should be of fish or seafood.

‡ No more than one lunch per week should be from the leaner cuts of beef, lamb or pork.

# Cooked or raw.

§ At least two dinners (preferably more) per week should be of fish.

[1] No more than two dinners per week should be from the leaner cuts of beef, lamb, pork or veal.

/ Vinegar, lemon juice, or a non-calorie dressing for salad portion.

// All or some of this may be used at meal time.

TABLE 4

New Coronary Disease Events* and Incidence in Study and Control Subjects Free of Coronary Heart Disease, 40-59 Years of Age, as of 11/30/67

	Experimental		
	Active†	Inactive‡	Control
Number of subjects	941	532	457
Years of experience	3,954	3,207	3,122
Confirmed new events	17	24	32
Incidence per 100,000 person-years of experience	430	748	1,025

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* As determined by the criteria of the New York Heart Association based on clinical, historical and electrocardiographic evidence.

† Experience accumulated while subject was in the status of regularly attending the clinic at specified appointment dates.

‡ Experience accumulated while attending study facilities annually or with successful regular contact by mail or phone since active attendance at panel or nutritionist sessions were discontinued. No professional supervision in this phase.

they are seen every week. Despite the concentration of personnel and effort in lowering serum cholesterol and reduction of weight, the results obtained utilizing the techniques of the Anti-Coronary Club study project can be the basis of preventive community medical programs to combat coronary heart disease. For high-risk screening, the practicing physician can utilize the serum cholesterol and triglyceride determinations. He can readily practice preventive medicine in his own office in an effort to reverse the risk factors affecting his patients.

The decrease in morbidity rate in the experimental group could not be ascribed to any change in cigarette-smoking habits; the Anti-Coronary Club Study protocol was limited to diet modification. It is recognized, however, that efforts to reduce other risk factors such as psychic stress and lack of physical activity could contribute further avenues to coronary heart disease control.

The American Medical Association has recognized the importance of controlling the level of serum cholesterol in high-risk groups and has suggested the need to control high serum-cholesterol levels observed in the young adult. The American Heart Association has repeatedly emphasized the preventive role of serum cholesterol-lowering diets and has recently indicated that appropriate dietary changes should be instituted for the public in general. The results described appear to be confirmed by other prospective diet-heart studies in progress, specifically by those of Leren, Turpenin and Birenbaum. There is, therefore, good reason to expect progress in reducing a paramount public health problem by implementing the knowledge at hand.

Chronic Condition

Let's diagnose the patient who
Gets pains when doctors' bills are due,
Excruciating pains that stab
His shoulder when he starts to grab
Some cash from out his pocketbook.
Oh, doctor, what an anguished look,
And what a throbbing of the neck
If he should try to write a check.
It shows that there's congestion, tightening,
A state of shock that's truly frightening.

If such a sickness needs a name
To give it proper place and fame,
Here's one (if you've a better, write us);
Disbursitis.

—Richard Armour: The Medical Muse, 1963.

Keeping Up To Date

A doctor picking up his car at a garage was highly indignant at the size of the repair bill. "All this for a few hours' work?" he protested. "Why, you charge more for your work than we of the medical profession do!"

"Well now," replied the mechanic, "that's just how it should be. You doctors have been working on the same old model since time began, but we've got to learn a brand-new model every year."*

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*Maxwell Droke: The Speaker's Handbook of Humor.

The Cardiovascular Risk

Associated with Different Levels and Types of Elevated Blood Pressure*

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THE ASSOCIATION BETWEEN elevated blood pressure found in over 17 million of our population and atherosclerotic cardiovascular disease has been thoroughly documented in the clinical situation, experimental laboratory and population studies.

Risk from Elevated Blood Pressure

The risk gradients from elevated blood pressure are reflected in the report[1] by the Society of Actuaries (Table 1). Mortality ratios increase sharply for both systolic and diastolic blood pressure. As the systolic pressure increases for any given diastolic pressure, the risk also increases, approaching two-and-a-half times—even when moderate blood pressures are considered. The same relationship holds for diastolic. The highest mortality ratio of two-and-a-half to three times is at the highest systolic-diastolic combination. Thus, either systolic or diastolic pressure is a measure of risk.

Risk from Selected Causes

Figure 1 shows the increased risk for the general categories: heart and circulatory diseases against vascular lesions of the central nervous system for different levels of blood pressure. When the systolic or diastolic blood pressure is slightly elevated, the risk is about one-and-a-half times; if both are elevated the risk jumps to about two-and-a-half times, further rising to three and six times at higher levels (though not marked elevations) for cardiovascular disease and strokes.

Hypertension vs. Normotension

The risk ratios are obviously dependent on

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*Presented at the Minnesota Symposium on Prevention in Cardiology, May 2-3, 1968 in Rochester, Minnesota.

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"end points," but as indicated previously these "minor" blood pressure elevations, so-called "borderline" or "high normals," both systolic and diastolic, are not innocuous.

The incidence data from longitudinal studies[2-6] are helpful. We have selected several from which data for both coronary heart disease and stroke are available (Figure 2). The incidence rate for hypertensives (BP ≥ 160/95) versus normotensives (BP < 140/90) is about two-and-a-half times that for coronary heart disease and five times that for thrombotic stroke in the Framingham Study; in the Los Angeles Study one-and-a-half and five times; and in the Chicago Study, considering only diastolic, three and four times.

Yet we know that elevated blood pressure alone may not increase the risk for coronary heart disease. For example, the Japanese have a high incidence of stroke associated with their high prevalence of hypertension, but they experience no excess of coronary heart disease.

Coronary heart disease is of multifactorial etiology; the risk of elevated blood pressure is potentiated by other factors such as high blood cholesterol level and heavy smoking. Individuals with high levels of these factors exhibit four to six times greater risk than those low in all three.[7] In fact, two thirds to three fourths of all men sustaining coronaries have cholesterol, high blood pressure, or both.[7,8]

The relationship between elevated blood pressure level and cardiovascular risk is by no means simple. Some people may live for years with an elevated blood pressure but with no overt manifestations. Others after a short period of elevated blood pressure develop marked physiologic changes.

What then are the relationships between patterns of blood pressure and alteration of target organs upon which the prognosis depends?

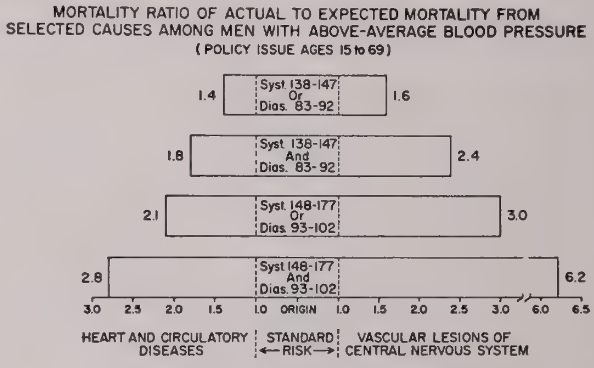
Is the increment or trend of blood pressure with age more important than a current reading? Stamler[9] has shown that diastolic blood pressure does not necessarily increase with age; Miall and co-workers[10] demonstrated that neither systolic nor diastolic pressure necessarily increases with age, but that those individuals with the highest blood pressure show the greatest increments.

TABLE I

Mortality Ratio (%) of Actual to Expected Mortality in Men According to Blood Pressure Level (Policy Issue Ages 15 to 69)

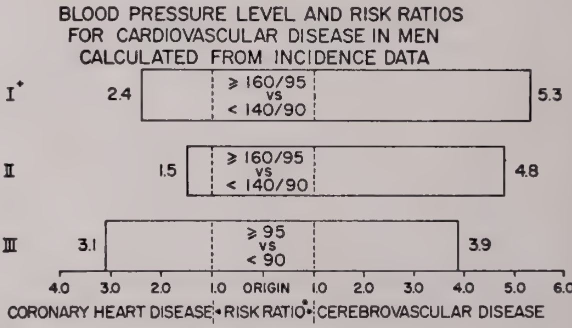
Systolic Blood Pressure	Diastolic Blood Pressure						
	48-67	68-82	83-87	88-92	93-97	98-102	Total
88-97	79						78
98-127	80	86	106	116	114		88
128-137	100	109	127	140	168	197	118
138-147	151	141	153	170	199	224	155
148-157		166	196	191	224	269	194
158-167		233	197	240	268	289	244
TOTAL	83	97	129	150	188	234	107

Source: Build and Blood Pressure Study, 1959 Society Actuaries



Source: Build and Blood Pressure Study, 1959, Society of Actuaries.

Fig. 1—Mortality Ratio of Actual to Expected Mortality From Selected Causes Among Men With Above-Average Blood Pressure (Policy Issue Ages 15 to 69).



*RISK RATIO = *Hypertensive Rate ÷ Normotensive Rate*

✦*Morbidity Ratio Used Rather Than Conventional Rate*

Source: I. Framingham - American Journal of Public Health. 55:1355, 1965.
II. Los Angeles Civil Servants - Journal of Chronic Diseases. 17:933, 1964 and Amer. Journal of Pub. Hlth. 56:191, 1966.
III. Chicago Utility Workers - "PREVENTIVE CARDIOLOGY", Stamler and J. Atheroscl. Res. 5:189, 1965.

Fig. 2—Blood Pressure Level and Risk Ratios for Cardiovascular Disease in Men. Calculated From Incidence Data.

Weight and Parental Longevity

Figure 3 demonstrates that the blood pressure of a group of young men in their mid-twenties is related, in part, to parental longevity but not to obesity.[11] However, as the group progressed through middle age, weight gain became increasingly important and interacted with parental longevity. This is depicted in the Table by the increased height in the first two columns when the men were in their 20s, and then the separation of the first and third columns representing weight gain as the men grew older. The column with both weight gain and short-lived parents demonstrates that men with both these characteristics definitely had the highest systolic blood pressure in later life. These findings were substantiated statistically by an analysis of variance and an estimation of the components of variance.

In general, obesity and other risk factors potentiate each other, and it is not unreasonable to presume that subjects with parental history of early death or vascular disease may be more vulnerable to blood pressure elevations, suggesting that familial and environmental factors do increase target organ susceptibility.

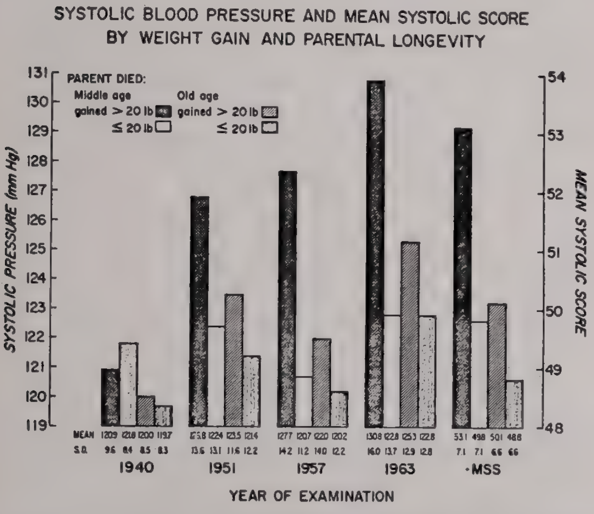


Fig. 3.—Systolic Blood Pressure and Mean Systolic Score by Weight Gain and Parental Longevity.
Source: Thousand Aviator Study.[11]

Patterns of Blood Pressure

Dustin[12] and Thurm[13] independently found that hypertensives who were able to reset their baro-receptors or remain normotensive after discontinuance of drug therapy had two factors in common, namely, mild hypertension before the onset of treatment and few cardiovascular complications.

Patterns of blood pressure other than increment may be important. Concerning blood pressure variability versus the average level, Pollack and colleagues[14] concluded that average blood pressures properly characterized the individual's blood pressure for risk appraisal. However, McKensie and Sheppard[15] felt that there was a distinctive effect of a previously elevated systolic pressure. Levy and others,[16] in a study of over 22,000 U. S. Army officers, found that men with transient elevations of blood pressure have as much as three to four times higher retirement rates and two to three times higher cardiovascular-renal mortality rates than the officers without this supposedly minor finding. A long-term study[17] also revealed that the increase in risk from coronary artery disease and cerebrovascular disease was higher for people with frequently elevated blood pressure and higher still for those with consistently elevated pressures for those of all ages. Sokolow and colleagues,[18] in a short-term study over several days with multiple measurements using a portable blood pressure apparatus, found that blood pressure variability did not relate to development of hypertensive complications which were mainly determined by the average level of arterial blood pressure. Thus, there is no simple answer to this question, in part because of the difficulties in determining blood pressure variability.

Threshold of Damage

Is there a critical point or threshold of blood pressure that damages different end organs, or is the relationship continuous for all? Also, are the associations with systolic blood pressure the same as those with diastolic?

In an attempt to identify some of the factors and interactions involved in the damage to target organs, we will report on data collected at four points in time on a cohort of initially normotensive men followed for 24 years.[19] We sought to relate trends and variability of blood pressure from early adulthood to middle age with target organ damage as manifest by heart size, electrocardiogram measurements, and pertinent laboratory measures. At the most recent examination the men were 47 years old. Systolic and diastolic blood pressures at ages 24, 35, 41, and 47 and blood pressure changes between these ages were related to other variables. We evaluated the effect of blood pressure on the basis of mean blood pressures over the entire period of study; a mean score representing overall rank in the cohort for the blood pressure evaluations; and a classification based on mean blood pressure at or above arbitrary levels (140 or 90) during any of the four examinations. Finally, we also used a measure of cardiac work, the systolic tension time. We analyzed the interactions and contributions of the various blood pressures through multiple correlations using the cardiovascular measurements as criterion variables and blood pressure plus a number of related measurements such as weight gain, skin-folds, smoking, and parental longevity as predictors (Table 2). In other words, we tried to predict things like heart rate at age 47 from previous parameters such as blood pressure change from age 24 to 47, weight change, lipids, etc. To be selected, each predictor must contribute something unique, e.g., if two blood pressures are correlated with the criteria only the one with the higher relationship would be selected. The other predictor would be selected only if it added something unique to prediction of the criterion variable.

TABLE 2
Multiple Correlations

Criteria	*Predictors*	*Predictors*
Fundus	Cas. Sup. Sys BP 63	Mean Diast BP
Glucose 2 Hr PP	Cas. Sup. Sys BP 40	Mean T Score Diast
Cholesterol	Cas. Sup. Sys BP 51	Diast Mean <90 >90
Uric Acid	Cas. Sup. Sys BP 57	Highest Diast BP
Log LIPO 20-400	△ Syst BP 40-63	Log Diast. Variance
Trans Diam HT	△ Syst BP 51-63	Diast Evaluation
Vital Capacity	△ Syst BP 40-57	Hematocrit
Heart Rate	Mean Systolic BP	Glucose 2 HR PP
QRS Front-Vect	Mean T Score Syst	Cholesterol
T Front Vect	SY Mean <140 >140	Uric Acid
Sigma Qrs	Highest Syst BP	Log LIPO 20-400
Sigma T	Log Syst BP Varian	Height 63
Max QRS Volt FP	Syst Evaluation	Skinfold Arm
Ratio T(I)/R(I)	Syst BP × Mean HT	Skinfold Back
AMP SI+SII+SIII	Diast BP 1963	Alcohol Amount
Amp SVI+RV5 or V6	Diast BP 1940	Cigarette Amt.
Max ST Aft. Ex.	Diast BP 1951	Heart Rate
	Diast BP 1957	Wt. Gain 1940-1963
	△ Diast BP 1940-63	Wt. 1963
	△ Diast BP 1951-63	Parental Longevity
	△ Diast BP 1940-57	

Measurements Used for Criterion and Predictor Variables in Multiple Correlations.

Multiple Correlations

Heart rate, fundus abnormalities, heart size, Sf 20-400 lipoproteins, two-hour post-prandial glucose, vital capacity and electrocardiogram measures of amplitude and frontal vectors at age 47 were a function of blood pressure and were independent of weight. Some variables such as fundus, heart size, vital capacity, 20-400 lipoprotein and ratio T/R in lead I related to blood pressure measurements taken as early as age 35. Other associations were not apparent until age 41 or 47.

Cumulative Multiple Correlations

Generally, blood pressure increments, mean blood pressures and measures of variability did not predict end organ change better than the most recent blood pressure, although for particular measurements they added unique information. For example, the highest diastolic pressure was the most important *blood pressure* predictor of frontal QRS Vector (Figure 4) although weight was the best predictor. Thus for predicting frontal QRS vector, body build and peak diastolic blood pressure were best. For the fundus (Figure 5) the variables chosen as predictors were the 1963 diastolic pressure and the alcohol intake; this

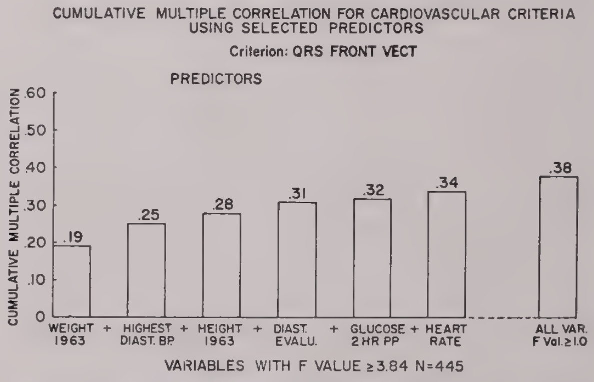


Fig. 4—Cumulative Multiple Correlation for Cardiovascular Criteria Using Selected Predictors. Criterion: QRS FRONT VECT

table illustrates that several patterns of blood pressure may have predictive value. For example, systolic blood pressure variability contributed something unaccounted for by the 1963 diastolic blood pressure, the best predictor. Parental longevity and cigarette smoking further added to the correlation. For the transverse diameter of the heart (Figure 6), though a number of variables are listed, only weight and mean diastolic blood pressure of those listed contributed substantially to the correlation coefficient. As expected (Figure 7), vital capacity related well to height and cigarette smoking, but also unexpectedly to a number of other measures, especially change in systolic blood pressure at age 24 to 47.

Stature and smoking both relate to the risk of coronary heart disease as well as to vital capacity. The fact that skinfold thickness and systolic blood pressure also act as predictors of vital capacity may indicate that the relationship noted between vital capacity and coronary heart disease may be mediated, at least in part, through these factors. In other words, vital capacity may be a risk factor only through its association with other factors and not through any inherent physiologic relationship. The commonly used electrocardiogram criteria for LVH ($SVI+RV_5$ or V_6) were independently related to the most recent systolic blood pressure, weight, cigarette smoking, and measures of blood pressure variability. It can be seen that various patterns of blood pressure may differ in importance in relating to criteria of end organ damage.

There is no marked discrepancy between systolic and diastolic blood pressures as predictors of other variables, but overall the diastolic pressures were better.

Furthermore, not all relationships were continuous (Figure 8). Putting all the variables in standard units it seems that those on the left differ primarily from those at the upper end of the blood pressure distribution; on the other hand, the ratio of the T wave to the R wave in Lead 1 differs primarily from those at the low end of the blood pressure distribution. The continuous relationships are apparent in the center of the slide. It may be that if we look at all end organs together the relationship is continuous, but for each individual parameter the association may be noncontinuous.

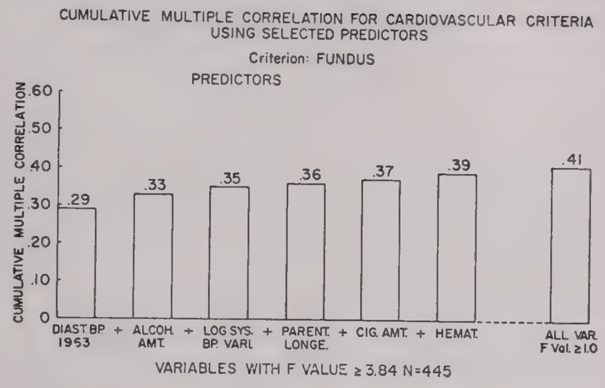


Fig. 5—Cumulative Multiple Correlation for Cardiovascular Criteria Using Selected Predictors.
Criterion: FUNDUS

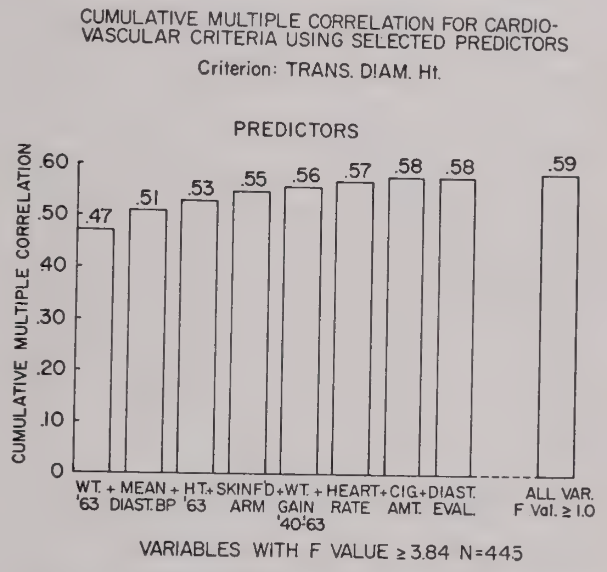


Fig. 6—Cumulative Multiple Correlation for Cardiovascular Criteria Using Selected Predictors.
Criterion: TRANS DIAM HT

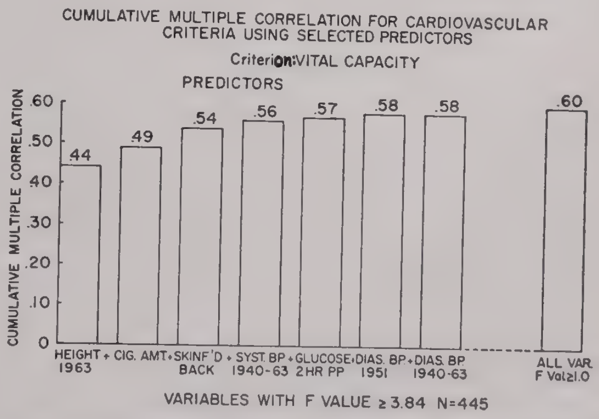


Fig. 7.—Cumulative Multiple Correlation for Cardiovascular Criteria Using Selected Predictors.
Criterion: VITAL CAPACITY

Concluding Summary

Development of atherosclerotic cardiovascular disease and subsequent mortality are obviously related to blood pressure levels. Target organ damage may be sustained at an early age with only moderate elevations of blood pressure. Recent studies[12,13] suggest that possible resetting of baro-receptors or other mechanisms after hypertensive therapy can be accomplished only if the therapy is started early and before cardiovascular complications. Blood pressure should be maintained at low levels preferably without a period of elevation of either systolic or diastolic. Not only should blood pressure be kept low, but attention given to concomitant variables such as diet, weight, smoking—alteration of which may potentiate the beneficial effects of reduction of blood pressure. Familial factors measured by parental longevity in our study, admittedly a gross index, did not materially aid our predictors; on the other hand, environmental factors, by virtue of influencing target organs, may be of critical importance in determining prognosis for hypertensives.

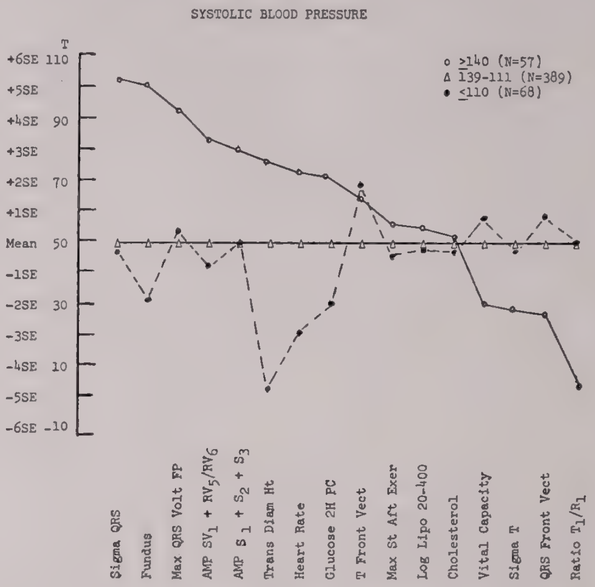


Fig. 8—T-Score Means of Trichotomized Blood Pressure Groups for Selected Variables. (T mean = 50, Std Dev = 10; T = $\frac{10}{SE_m}$ (M-μ) + 50; SE$_m$ = $\frac{\sigma}{\sqrt{N}}$)

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Out of a hundred diseases, fifty are caused by our own faults and forty by our carelessness.—Paolo Mantegazza

Gross Obesity*

The Cardiovascular Consequences

JAMES K. ALEXANDER, M.D.†
Houston, Texas

I would like to address myself to three questions: First, what are the circulatory effects of gross obesity? Second, how reversible are these effects once manifest? Third, what can be done to achieve weight reduction in very obese subjects? The last is the most difficult question and the one about which we know least.

Circulatory Effects of Gross Obesity

Gross obesity has easily demonstrable circulatory effects. It leads to an increase in the circulating blood volume, to an increase in the cardiac output and to an increase in blood pressure in a sizable percentage of such subjects. Because of the increase in the volume and pressure work load on the heart, the work of the heart is greater. Cardiac hypertrophy usually develops, and ultimately congestive heart failure may supervene.

Increased Blood Volume

Some data that we have collected in such subjects on blood volume are shown in Figure 1. As the amount of weight over ideal increases, the circulating blood volume tends to

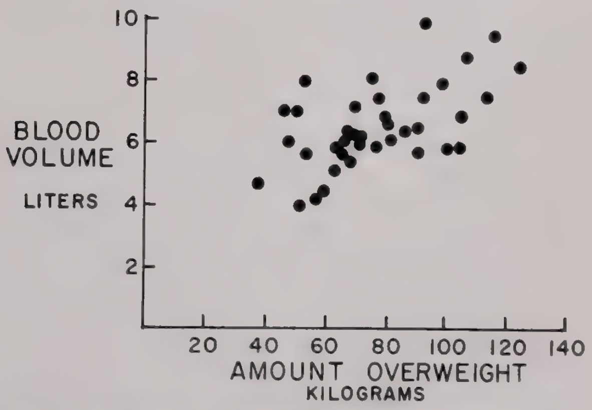

Fig. 1—Relationship between blood volume and amount of excess body weight in 40 very obese subjects.

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*These studies have been supported by U. S. Public Health Service Grants HE-3006 and HE-5435, and the Houston Heart Association.

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†Professor, Baylor University College of Medicine, Department of Internal Medicine, Texas Medical Center.

rise, and when there is a gain of 200 pounds, the blood volume is about double the normal.

High Cardiac Output

Figure 2 shows what happens to the amount of blood that the heart must pump under these circumstances. There tends to be a correlation between the cardiac output and the increase in body weight. If you are 200 pounds overweight, at rest your heart pumps about twice what the heart of the subject at ideal weight would have to pump.

Elevation of Blood Pressure

In about two thirds of these subjects blood pressure is elevated; however, in the remainder blood pressure is normal. Hence we may conclude that, while obesity does predispose to hypertension, the fact that an individual is grossly overweight does not necessarily mean that he is also hypertensive. These data are based on direct intra-arterial pressure measurements. If the amount of blood that the heart pumps per unit time increases and if the pressure under which the blood must be delivered to the systemic circulation is elevated, the work of the heart is increased.

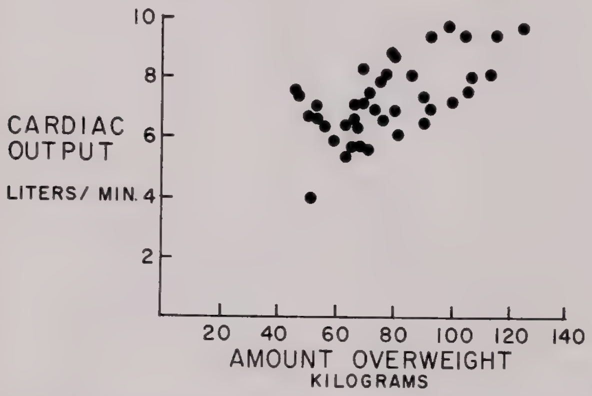

Fig. 2—Relationship between cardiac output and amount of excess body weight in 40 very obese subjects.

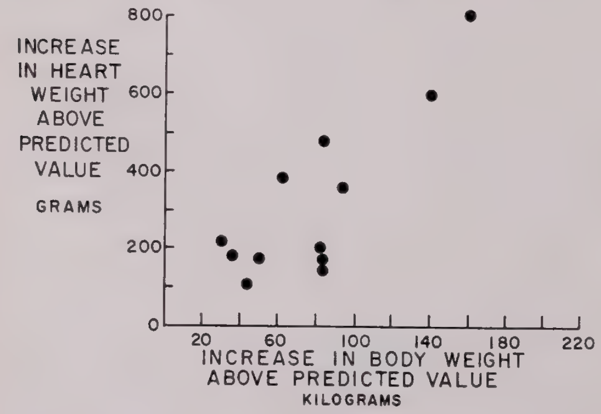

Fig. 3—Relationship between increment in heart weight and body weight above predicted values in 12 very obese subjects.

Enlarged Heart

These patients tend to have large hearts. Figure 3 shows the results of a study that we did some years ago. The hearts of a selected group of such very obese subjects were examined at autopsy. The heart weight tends to be increased as the body weight increases. This roughly linear relationship must tend to plateau, because since then we have carried out an autopsy on a 700-pound man and his heart weight was something of the order of 400 to 500 grams over the predicted level. Figure 4 shows the heart of a patient six feet tall, weighing 500 pounds at death. The tremendous hypertrophy of the left ventricle, the ventricular septum, and the right ventricle can all be seen. The left ventricle is about twice normal thickness. The total heart weight was 1100 grams, about 800 grams over the predicted weight. The increase in weight is clearly the result of myocardial hypertrophy and not an increase in epicardial fat or fatty infiltration of the myocardium.

Congestive Heart Failure

More recently we have surveyed 3,500 consecutive autopsies in the Veterans Administration Hospital in Houston, where we found nine patients 300 pounds in weight or over at the time of death, all of whom had gross and microscopic evidence of congestive failure: that is, systemic and pulmonary congestion. All had cardiac hypertrophy involving the left ventricle and in two cases involving the right ventricle. Six of these patients had clinical manifestations of cardiac failure prior to death; hence in very obese subjects, cardiac failure is frequent and plays a significant role in the demise of the patient.

Reversibility

In nine subjects we have been able to achieve weight loss varying from 85 to 185 pounds over periods of observation varying from four to 36 months. In all three instances where the pressure was elevated it did tend to fall to or toward normal following weight reduction. In those in whom the blood presure levels tended to be normal, there was a small reduction. Blood volume and cardiac output fell toward normal in every instance.

However, our data suggest that over the period of several months to three years that we observe these patients there was no tendency to regression of hypertrophy; there is little change in the filling pressure of the left ventricle, and it rose on exercise just as much as it did before weight reduction. Therefore we have no evidence to indicate that diminished myocardial compliance or ventricular hypertrophy regress with weight reduction.

Weight Reduction

In order to achieve weight reduction in these very obese subjects we found it necessary to hospitalize them under direct observation for periods of several weeks or months. Among well over 100 patients in an eight-year period, in only a few instances has significant weight reduction been achieved on an out-patient basis. We have had no success whatsoever using appetite-depressant drugs. If the patient is motivated to lose weight, he will do it irrespective of drugs. Within a year after discharge from the hospital, a patient with reduced weight will frequently return at control weight. In these very obese patients the approach to weight reduction is difficult and often discouraging. These patients commonly have a genetic or familial predisposition. Perhaps a coordinated approach by the internist, the psychiatrist, the dietitian, the social worker, and a variety of para-medical personnel brought to bear in a community effort may be more productive. It is necessary to change the entire way of life.

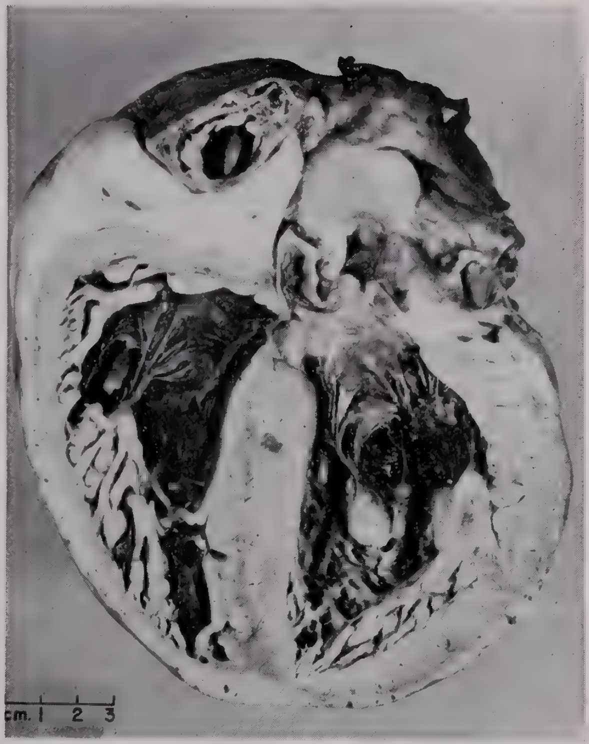

Fig. 4—An example of marked ventricular hypertrophy in an extremely obese patient with a body weight of 497 pounds. The heart weight is 1100 grams. There is gross increase in the thickness of both ventricular walls, particularly the left. Note that epicardial fat is not especially increased.

Conclusions

Management of obesity presents a great challenge. Perhaps those of us who are interested can best perform our function by educating the physician and the public to the consequences of obesity, so that obese individuals will be better motivated to lose weight. Prevention certainly cannot be overemphasized. Our immediate goal is to make the physician and the patient conscious of the problem.

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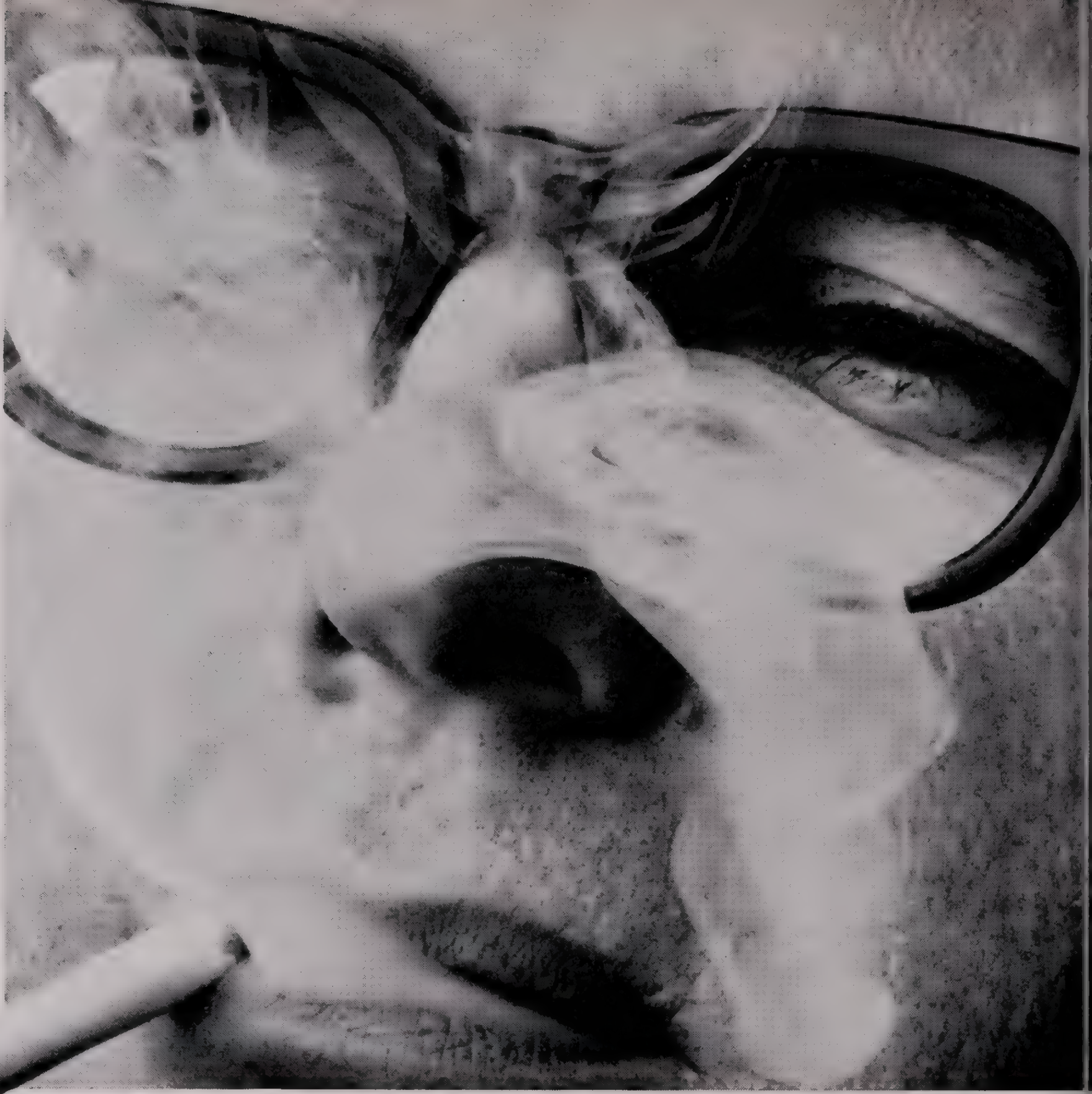
Overweight

Many a middle-aged woman is thick and tired of it.



Clues to PVD

The heavy smoker with vasospasm

He may be comparatively young or approaching middle age. Typically, he is a heavy cigarette smoker—a pack or more a day for a number of years. Whether smoking is a causative or an important exacerbating factor in peripheral vascular disease is still under discussion. But the vasoconstrictive effects of nicotine are firmly supported by a substantial body of laboratory and clinical evidence, and the close association is now generally accepted.

Thus, a history of heavy smoking coupled with vasospasm may serve as warning signals to the physician. When a diagnosis is established, therapeutic measures are directed toward increasing the local circulation, and appropriate management of the patient's general medical needs should be instituted. These include the important safeguards of keeping warm and refraining from smoking.

Before prescribing Roniacol Timespan (nicotinyl alcohol tartrate), please consult complete product information, a summary of which follows.

Indications: Conditions associated with deficient circulation; *e.g.*, peripheral vascular disease, vascular spasm, varicose ulcers, decubital ulcers, chilblains, Meniere's syndrome and vertigo.

Caution: Roche Laboratories endorses caution in the administration of any therapeutic agent to pregnant patients.

Side Effects: Transient flushing, gastric disturbances, minor skin rashes and allergies may occur in some patients, seldom requiring discontinuation of the drug.

Dosage: 1 or 2 Timespan Tablets morning and night.

How Supplied: Timespan Tablets—150 mg nicotinyl alcohol in the form of the tartrate salt —bottles of 50.

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for relief of ischemic symptoms

Convenience of b.i.d. dosage—sustained-release Timespan Tablets usually provide prolonged relief of ischemic symptoms with two doses daily.

Smoothness of onset—the action of Roniacol (nicotinyl alcohol) is smooth and gradual in onset, rarely causing severe flushing.

Selectivity of action—relaxes the musculature of peripheral blood vessels.

High degree of safety—side effects seldom require discontinuation of therapy.

Mild ulcerative colitis may be triggered here...

In mild ulcerative colitis, a number of factors can precipitate an attack: for instance, dietary indiscretion, such as eating raw foods, or emotional overreaction, such as that aroused by financial difficulties. No matter what causes the patient's sensitive colon to "act up," he soon suffers from acute discomfort...and often, from anxiety and apprehension as well. Such patients frequently respond well to adjunctive dual-action Librax® therapy.

Librax combines, in a single convenient capsule, the well-known antianxiety effect of Librium® (chlordiazepoxide HCl) and the dependable anticholinergic/antispasmodic effect of Quarzan® (clidinium Br). Therefore, as Librax helps to relieve the patient's excessive anxiety and reduce his overreaction to stress, it also, at the same time, helps to control hypersecretion and hypermotility, thus relieving spasm and abdominal discomfort.

With Librax, the dosage schedule is simple: 1 or 2 capsules, t.i.d. or q.i.d., will in most cases bring the patient significant relief of both the emotional and physical elements that contribute to his psychovisceral disorder.

Before prescribing, please consult complete product information, a summary of which follows.

INDICATIONS: Indicated as adjunctive therapy to control emotional and somatic factors in gastrointestinal disorders.

CONTRAINDICATIONS: Patients with glaucoma; prostatic hypertrophy and benign bladder neck obstruction; known hypersensitivity to chlordiazepoxide HCl and/or clidinium bromide.

WARNINGS: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reporte on recommended doses, use caution in administering Librium (chlordiazepoxide hydrochloride) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potentia benefits be weighed against its possible hazards As with all anticholinergic drugs, an inhibiting effect on lactation may occur.

PRECAUTIONS: In elderly and debilitated limit dosage to smallest effective amount to preclude development of ataxia, oversedation or confusion (not more than two capsules per day initially; increase gradually as needed and toler-

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ion and acute rage) have been reported in psy-
hiatric patients. Employ usual precautions in
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ending depression; suicidal tendencies may be
resent and protective measures necessary. Vari-
ble effects on blood coagulation have been
eported very rarely in patients receiving the
rug and oral anticoagulants; causal relation-
hip has not been established clinically.
ADVERSE REACTIONS: No side effects or
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specially in the elderly and debilitated. These
are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally with chlordiazepoxide hydrochloride, making periodic blood counts and liver-function tests advisable during protracted therapy. Adverse effects reported with Librax are typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy and constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diet.

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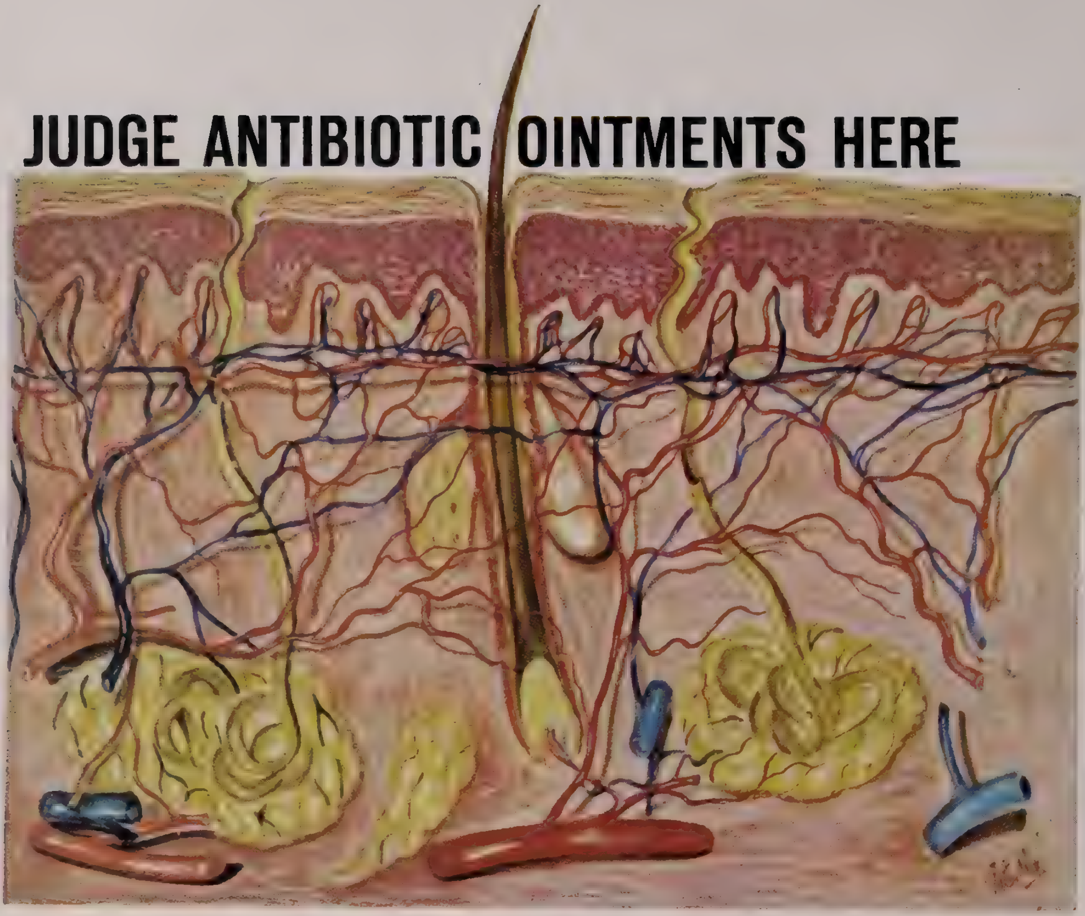

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Veterans Multiclinic Trial of Drug Treatment in Hypertension[*]

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The value of antihypertensive drug treatment in severe or malignant forms of hypertension has been widely accepted, but the value of drugs in mild and moderate hypertension has been disputed. There has been no question that agents are at hand which effectively lower blood pressure; but a more basic question has been posed: Is the reduction in blood pressure really beneficial; does it significantly prevent *morbidity* in patients with less than severe hypertension? It became apparent by 1963 that adequately controlled, prospective studies of sufficient sample size were needed to evaluate this question. The Veterans Administration Cooperative Study Group on Antihypertensive Agents therefore commenced an investigation of this type in early 1964 under the chairmanship of Dr. Edward Freis of Washington. Twelve Veterans Administration Hospitals pooled their resources in this study; the participating physicians were either Veterans Administration-based or clinical faculty members of the associated medical schools who thought the issue was important and the time ripe for such a study.

Randomized Study

The design of the trial is shown in Figure 1. Candidates for the study were detected among patients admitted to these 12 hospitals for a variety of reasons. Following initial hospitalization for work-up and evaluation, patients who were tentatively eligible were discharged to the clinic on known placebos where they were followed for a trial period of two to four months. Those who qualified for admission to the study on the basis of the findings during the initial hospitalization and during the trial period were then randomized into the study to receive either active drugs as shown here or placebos of these three drugs. Reduction of doses or omission of offending agents was permitted in case of severe side effects or excessively low blood pressure.

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Presented at the Minnesota Symposium on Prevention in Cardiology, May 2-3, 1968 in Rochester, Minnesota.

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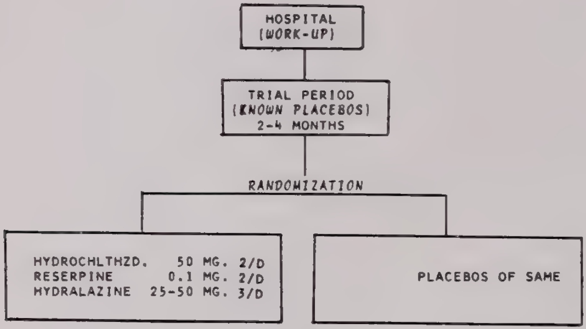

Figure 1

Severity Index

Those patients whose diastolic pressure during the fourth through the sixth hospital day averaged from 90 to 129 mm Hg and whose severity index of hypertension was less than 16 were the prime candidates for the study. The severity of the hypertension was graded on a numerical scale in which hospital basal diastolic blood pressure, and abnormalities in the optic fundi, central nervous system, heart and kidneys were combined to obtain a total "severity" index. We excluded patients who had a history of grade III or IV funduscopic changes, cerebral or subarachnoid hemorrhage, dissecting aneurysm, congestive heart failure persisting despite digitalis and mercurials, BUN ≧ 60 mg percent, and also patients with acute hypertensive-encephalopathy or a history of the same in the past. Patients with terminal diseases unrelated to hypertension, such as malignancies, were also excluded. Finally, in an effort to keep the drop-out rate as low as possible we excluded patients of doubtful reliability, such as most alcoholics and vagrants.

Reliability Tests

Further exclusions from the study proper were made during the pre-randomization trial period when the patient received placebos known to the doctor but not to the patient. During the trial period the patient was seen at monthly intervals in the clinic. In order to qualify for randomization, the average of the diastolic blood pressures observed in the clinic while on known placebos had to be in the range of 90 to 129 mm Hg. In addition, there had to be two *successive* clinic visits, in which the patient exhibited no violations with regard to several different tests of reliability. These reliability tests were: keeping scheduled clinic appointments; pill counts; and urine fluorescence tests. The pill counts had to be in an acceptable range. The fluorescence test was based on the ability of riboflavin to produce a bright fluorescence of the urine, riboflavin being incorporated in the tablets.

Risk Factors

The study started in the Spring of 1964 and by the end of 1966, 421 patients had been enrolled. By this time it became apparent to the reviewing biostatisticians that a rather large number of complications were clustering in one segment of the placebo-treated group and very few complications in the comparable segment of the actively-treated group. Various indices were used in an attempt to separate out the patients with the highest risk rate of these adverse events. Among the criteria tested were blood pressure, funduscopic changes, cardiac changes, central nervous system scores and renal severity scores. It was found that the average diastolic blood pressure measured by the doctor in the clinic during the placebo trial period provided by a considerable margin the best prognostic indication of future trouble. Optimal separation between higher-risk and lower-risk groups was obtained at a diastolic level of 115 mm Hg, those at this level and above being the high-risk group. It is this latter group with average clinic diastolic pressures of 115 mm or more during the trial period on *known placebo treatment* whose results are described. All of these patients were removed from the study one year ago and placed on known active drugs. The lower-risk group, with trial period diastolics below 115 mm, are still in the randomized double-blind trial.

The High-Risk Group

Background Characteristics

The high-risk group included 70 patients randomized on placebos and 73 on active drugs

(Table 1). How comparable were the two groups? With regard to race, the percentage of Negroes was slightly higher in the actively-treated group. With respect to prevalence of cardiac symptoms, the two groups were essentially similar. Note the high proportion of patients with enlarged hearts. However, the numbers were essentially the same in the two groups.

TABLE I
Background Characteristics

	Number	
	Placebo	Active
Total	70	73
Caucasian	35	31
Negro	35	42
Cardiac symptoms	22	21
Ungerleider abnormal	31	29
ECG—LVH	22	24
Prior CVA	5	6
Diabetes present	5	8

Table 2 shows that the two groups were also similar in other key characteristics. We have concluded that placebo and drug-treated patients were comparable in all major respects.

Blood pressure was successfully reduced in the actively-treated patients.

TABLE 2
Background Characteristics

	Averages	
	Placebo	Active
Age (yrs.)	51	50
Weight (lbs.)	183	185
Hosp. diast. P (mm.Hg)	106	107
Pre RX Clinic B.P.	187/121	186/121
Fundi grade	1.2	1.3
Renal grade	0.5	0.3

Blood Pressure Changes

Figure 2 shows the distribution of blood pressure changes at the end of the fourth month following randomization.

Ninety-four per cent of the actively-treated patients showed a reduction of diastolic blood pressure, the average fall being 28 mm Hg. The average diastolic pressure dropped from the pre-randomization level of 121 to 93 at four months.

In the placebo group half the patients showed no change. Of those who showed a change, more had a decrease in blood pressure than an increase. Observations at later time periods showed that the average diastolic blood pressure in the actively-treated group remained down, while the average blood pressure in the placebo group stayed closer to the initial level.

Because we began enrolling patients in the study in the Spring of 1964 and stopped the double-blind study on high-risk patients one year ago, we have a variable length of observation per patient — ranging from one to 34 months. The period of postrandomization follow-up was shorter in the placebo group, averaging 16 months, as opposed to 21 months in the actively-treated patients. The reason for the difference is the large number of placebo-treated patients who were removed from protocol and placed on active therapy because of complications.

Mortality

The first and simplest analysis of results pertains to the mortality observed. There were four deaths, all associated with cardiovascular complications (two dissecting aneurysms, one

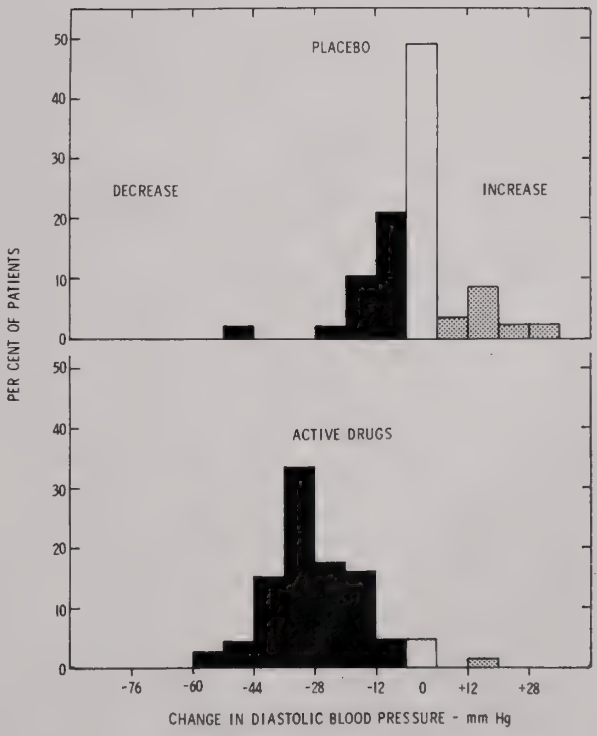

Figure 2

ruptured abdominal aneurysm and one sudden death). All occurred in the placebo-treated patients.

Morbidity

In defining the main purpose of the study, cardiovascular morbidity, two classes of morbid events were established early: Class A consisted of hypertensive complications and Class B of atherosclerotic complications or congestive heart failure responding to digitalis.

Class A events required removal of the patient from protocol treatment with permission to treat with known active drugs. Included in this category were the following: cerebrovascular or subarachnoid hemorrhage; dissecting aneurysm; a two-fold increase of blood urea nitrogen (BUN) to levels above 60 mg/dl; funduscopic evidence of grade III or IV hypertensive retinopathy (multiple striate hemorrhages or soft exudates in more than one quadrant, or bilateral papilledema); and congestive heart failure if it could not be controlled with digitalis, restricted activity, and occasional mercurial diuretics. A persistent clinic diastolic pressure of 140 mm or more followed by rehospitalization basal pressure of 130 mm Hg was also counted as a Class A event because of our apprehension that another of the Class A events just listed was imminent.

On the basis of the criteria described above, ten placebo-treated patients had Class A morbid events (Table 3). There were no Class A events observed in the actively-treated patients. Five of the events in the placebo group were based upon optic fundi observations and five were other events. Follow-up of these various patients after termination from the study has shown that eight had reversible complications—their funduscopic and cardiac abnormalities disappeared with treatment; or, in the case of the patient with marked elevation of blood pressure, the blood pressure came down with treatment with known drugs.

TABLE 3

Class A Events (Placebo)

Fundi—hem. & papilledema	2
Fundi—hem. & soft exudates	2
Fundi—bilat. striate hem.	1
CHF plus bilat. striate hem.	2
Cerebral hem.	1
Elevat. BUN to 71 mg %	1
Rehosp. basal diast. av. 136	1

TABLE 4

Treatment Failures

Placebo	
Fundi. Single soft exudate	1
Fundi. hem & exud. but diabetic	1
BUN 70 mg % but diabetic	1
Creatinine 1.1 to 3.0 in young patient	1
Clinic diast. 140-150 but hosp. diast av. < 129	2
CV thrombosis. Severe paralysis	1
Active	
Hyperglycemia and depression	1

Treatment Failures

During the study it became necessary to account for an additional category of terminating events called "Treatment Failures." In such cases, the strict criteria for a Class A event was not met, but removal from protocol seemed necessary to the participating physician on ethical grounds.

There were seven "Treatment Failures" in the placebo group. These are detailed in Table 4. The only "Treatment Failure" on active drugs was of a very different character—a patient who developed serious drug reactions and was removed from the study.

There was considerable discussion as to what to do with these cases in the analysis. It appeared best to report them as marginally contributing to the overall assessment of the benefit of therapy. We thought this appropriate because it seemed likely that some of these patients would have been on the verge of Class A events, perhaps catastrophic ones, had they not been removed from the study. We are, however, reporting these in a separate category.

Class B events were those judged to be more related to atherosclerosis than to hypertension. All patients who sustained such events continued in the study. There were six in the placebo group as compared to one of the actively-treated patients. Two placebo patients had myocardial infarctions but recovered; two developed congestive heart failure which responded to digitalis and other routine measures, and there were two cerebrovascular complications. The sole actively-treated patient developed hypotensive symptoms immediately following randomization and developed a hemiparesis. He recovered from the hemiparesis and was later managed without symptoms on lower doses of protocol drugs.

Discussion

Most long-term clinical studies are troubled by losses. In examining our data to determine whether the dropouts had a significant influence on the results, we applied a most rigorous test. We assumed that the seven losses from the placebo group would have had no adverse events if they had stayed. Conversely, we assumed that all five of the losses from the active-treatment group were headed for trouble and would have had a Class A or B event if they had stayed under observation and treatment. Yet even these rigorous and rather improbable assumptions yielded a score of 27 to 7 ($P < 0.001$) in favor of treatment instead of the *observed* 27 to 2.

This is a report of a study that ended much earlier than anticipated, a study discontinued for ethical reasons with fewer patients and a shorter observation period than planned. It had been agreed at the outset that as the study progressed the accumulation of results would be kept in the hands of the reviewing statistician group and not revealed to the participating physicians unless decisively favorable or unfavorable evidence emerged requiring action. The statistician group, therefore, periodically examined the accumulated findings. To avoid making hasty judgments, the action limits were set well below the 1% level of significance. When the evidence grew to the extent reported here, the reviewing statisticians sought the advice of an independent clinical investigator who concurred that it was time to discontinue the trial among the high-risk patients.

Concluding Summary

A controlled clinical trial of the long-term usefulness of blood pressure lowering agents in preventing morbidity among male patients with mild to moderate hypertension was begun early in 1964. Random assignment of patients to treated or placebo groups was employed. The study was conducted on a double-blind basis. Criteria for most assessable adverse events were specified in advance. To minimize dropouts, careful screening, including a trial period, was employed before admission to the study proper.

A clear-cut difference between those treated with placebo and drug emerged in a rather short span of time for patients with moderate hypertension (clinic diastolics 115 to 129 mm Hg). The difference was this: only *two* adverse events occurred in the group of 73 drug-treated patients, 27 events occurred among the 70 placebo-treated patients.

It's the Law

The Right of Access To Medical Records

The Minnesota State Supreme Court amendment of the Rules of Civil Procedure changed the status of medical privilege which has existed between physician and patient. Rule 35.03, entitling Waiver of Medical Privilege and Rule 35.04, entitling Medical Disclosures and Depositions of Medical Experts, became laws effective February 1, 1968.

A Code of Cooperation has been approved by the Minnesota State Medical Association, Minnesota Hospital Association, Minnesota Association of Medical Record Librarians and Minnesota State Bar Association. The purpose of this Code is to promote understanding and cooperative action between the medical, hospital, and legal professions to provide medical information to those persons authorized to receive it; also, to produce records for court or administrative proceedings in an efficient and inexpensive manner with minimum expenditure of time by all persons concerned. Accordingly, the right of access to medical records with proper authorization is a law requiring cooperation by the medical profession.

Donald C. Mac Kinnon, M.D.
Chairman, Medical Advisory Committee

FEATURE SPECIAL

Paget-Schrotter (von Schrotter) Syndrome

This syndrome consists of sudden onset of pain, tenderness, and swelling of an upper extremity, a result of thrombosis of the axillary vein. It was described by Paget in 1875 and by Schrötter in 1884. The condition occurs in otherwise healthy individuals between the ages of 18 and 50 years with a greater preponderance for the male.

The initial symptoms are followed by nonpitting edema of the arm and occasionally of the shoulder and lower part of the neck. The right arm is most frequently involved. Superficial veins are distended and a deep thrombosed vein is usually palpable. Trauma is thought to be an important etiologic factor, although the syndrome may occur in a period of chronic cardiac failure. Differential diagnosis should exclude such conditions as thrombophlebitis migrans, an aneurysm of the aorta, and metastatic carcinoma.

The course of the disorder is benign; subsidence of the thrombosis normally occurs within two or three weeks even with conservative local treatment. Anticoagulant therapy is usually indicated as a safeguard as well as to expedite recovery.

Durham, Robert H.—Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York

Shakespeare's Doctors

Dr. Butts

Henry VIII's physician, Dr. Butts, appears in no professional role in the play "Henry VIII." Instead, we see him acting only as loyal political henchman to the King: just happening, either by chance or contrivance, to be in the right place at the right time to observe the Archbishop of Canterbury, Cranmer, demeaned by the councilors: an indignity Butts later reports to the King.

That Dr. Butts was not just a fictional character, however, but a licensed M.D. we learn from Goodall's Epistle Dedicatory: "Dr. William Butte, Fellow of Gonville Hall, in Cambridge, and Physician to King Henry VIII, was Anno Domini 1529, admitted into the College of Physicians. Upon which he was required to subscribe to the due observation of the Statutes of the College, and to give his promise to use his best endowments for advancing the honour and perpetuity thereof."

Editor's Note: Shakespeare's slight change in the spelling of the doctor's name is defensible on grounds of poetic license.

Civilization

If Aristotle came to life again, my guess is that what would impress him most in our civilization would not be our comforts and our gadgetry, but the progress made over the centuries in advancing basic science. Perhaps the two things that would trouble him most would be the difficulties that now stand in the way of the man who wishes, as he wished, to take all knowledge for his province, and the low standard of political competence achieved by the average American citizen.

J. P. Baxter

A big man is not one who makes no mistakes, but one who is bigger than any mistakes he makes.—Nuggets

Reducing Elevated Blood Pressure

Experience Found in a Community*

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J. GORDON BARROW, M.D.‡
Atlanta, Georgia

A RANDOM SAMPLE of a middle Georgia community was surveyed by door-to-door questionnaire and blood pressure measurements. All individuals with an average systolic blood pressure greater than 160 and/or average diastolic blood pressure greater than 95 were identified. Their awareness of their elevated blood pressure and any history of previous treatment for high blood pressure were determined. It was found that approximately 42% of those with elevated blood pressure were unaware of it and that only 30% of those aware of it were currently under treatment for this condition. Of those under treatment, approximately half had average blood pressures below 160 systolic and below 95 mm diastolic on the day of the survey, or possible "good blood pressure control." It was concluded that 15% of those with high blood pressure in this community were "under good control" as evidenced by the level of their blood pressure. The records of the private physicians of these subjects with elevated blood pressure were surveyed for the preceding three years. It was found that the doctors lost track within three months of 56% of the patients that they had begun on treatment, and we suspect that these patients discontinued treatment within the same period.

Follow-up Studies

We desired to see if home follow-up by a public health nurse with instructions as to the nature and care of high blood pressure, plus frequent checks of high blood pressure at home, plus re-emphasis of the importance of taking medication regularly, would improve these findings. Two hundred twenty suitable subjects of the original 630 with high blood pressure divided themselves by choice into a volunteer home follow-up group (88 subjects) and

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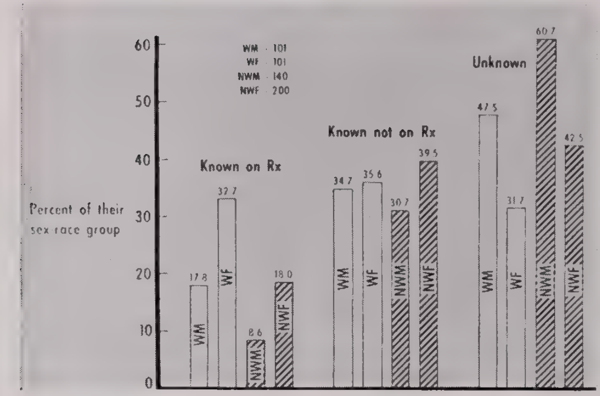
*Presented at the Minnesota Symposium on Prevention in Cardiology, May 2-3, 1968 in Rochester, Minnesota.

†Director, Cardiovascular Disease Control Service, State of Georgia, Department of Public Health.

‡Cardiovascular Disease Control Service, State of Georgia, Department of Public Health.

TABLE 1

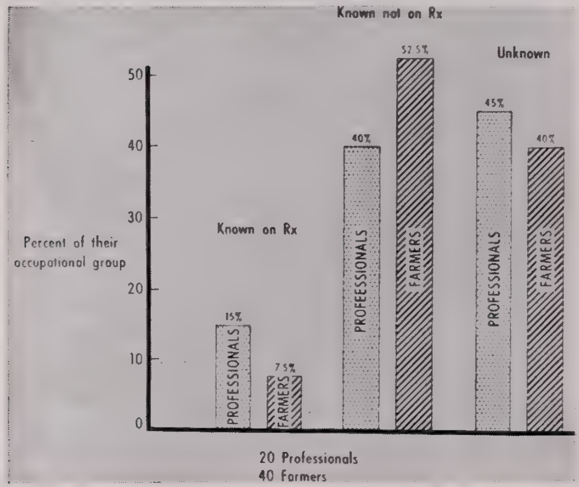


A comparison of three groups identified in a door-to-door blood pressure survey in Baldwin County. Georgia, by sex and race;

1. "Known on Rx": those who were aware of their elevated blood pressure and were currently taking medication for it.
2. "Known not on Rx": those who were aware of elevated blood pressure in the past but were not currently on treatment, (i.e., had discontinued treatment).
3. "Unknown": those who were found to have elevated blood pressure that day (greater than 160 mm Hg systolic and/or greater than 95 mm Hg diastolic) and had never known before that they had an elevated blood pressure.

WM = white male
WF = white female
NWM = non-white (negro) male
NWF = non-white (negro) female

TABLE 2



A comparison of two different occupational groups;

"Professionals" (physicians, dentists, lawyers, educators and clergymen). "Farmers"—full time occupation as self-employed farmers, by knowledge of and treatment of elevated blood pressure when originally surveyed.

a non-volunteer group (132 subjects). A public health nurse then visited the volunteers at home at regular intervals, persuaded them to go to the doctor for diagnosis and treatment and, if they were begun on medication for their blood pressure, attempted to keep them on the medication. On the average, it took two to three home visits to persuade the subjects that their blood pressure was indeed high and that they needed to see a physician for treatment. Also during the 18-month follow-up period, most of the patients had to be re-started on their medication at least once and frequently two or three times because their prescriptions ran out, or they "felt better," or they just neglected to take their medicine.

Two years after the survey the home follow-up group was compared with the non-volunteer group with regard to blood pressure level and to whether or not they were on treatment. Two years later after the entire program ended, both groups were re-surveyed to check on their persistency.

The Groups

Table 1 compares the sex and race distribution of three groups at the end of the original community survey: 1, Those that knew they had high blood pressure and were on treatment; 2, those that knew they had high blood pressure and were not on treatment; 3, those who were unaware of their elevated blood pressure. It can be seen that women are more aware of their elevated blood pressure than men and that Negroes are less likely to be under treatment than whites. Also it is evident that in both sexes and races there are very high percentages not on treatment: probably a typical distribution of the population with regard to visiting doctors' offices and following instructions. The first group are the "faithful" patients appearing in clinics and offices conscientiously; the second group come in occasionally for acute illness, and the third group are probably rarely seen in the physicians' offices or in clinics.

The Occupational Groups

Table 2 shows that in both professionals (doctors, lawyers, teachers, ministers) and farmers, there is a very large reservoir of untreated hypertension. This would indicate that educational and social levels are not all important factors in regard to awareness of high blood pressure.

The Non-volunteer Group

Table 3 shows what happened to the "non-volunteer group" of 132 hypertensives first surveyed in 1964, who were told that they had high blood pressure and were advised to seek treatment. Re-surveyed in 1966 and then again in 1968, it can be seen that the initial survey doubled the number under treatment in this group, but that when the study ended in 1966 and the public health team left the community, the number declined to approximately 35%.

The Home Follow-up Group

Table 4 shows similar findings in the "home follow-up group." This group (88 subjects), when first surveyed in 1964, showed only 25% under treatment with 15% having good blood pressure levels. By the use of home follow-up by the public health nurse with referral to a physician, education about the nature of hypertension, and reminders to take their medication, 86% were brought under treatment, of whom 80% had "good control" (diastolic levels below 95 on the average). However, when the nurse visits ended in 1966 and the subjects were left to their own devices until 1968, only 55% in that year were under treatment, with only 29% having "good control" as evidenced by their blood pressure at home.

Conclusions

There is a large reservoir of untreated high blood pressure in this population.

Forty-two percent of this reservoir is unaware of its elevated blood pressure.

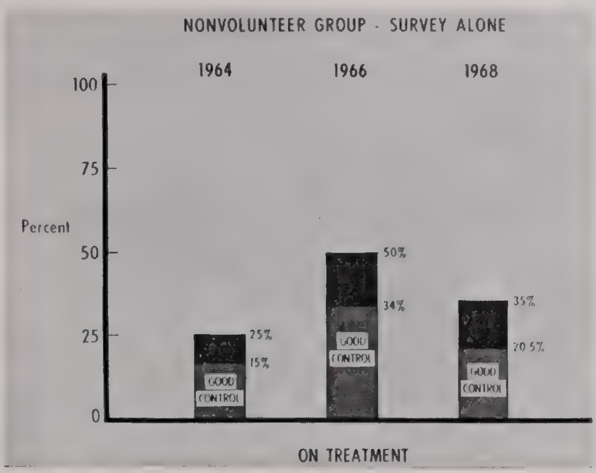
Most patients begun on treatment by their private physician are ignorant of the labile nature of high blood pressure, of its lack of symptoms and of the necessity of continuous follow-up and treatment.

Any successful program for control of high blood pressure in a community must be a continuous life-long program, must provide easy access and inexpensive or free blood pressure measurements, and probably should provide for free medication for that section of the population who feel they are unable to afford this medication.

The major reason for failure to control high blood pressure is failure to take medication.

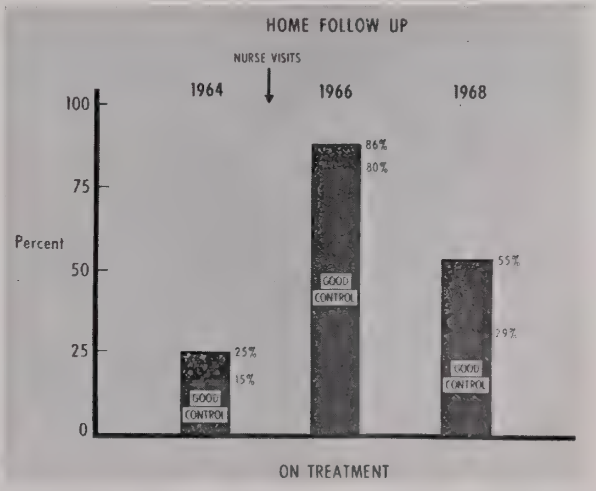
It is surmised by our study group that these results are not peculiar to Georgia but are likely to be found in other regions or countries, even those that have better educated and more affluent populations.

TABLE 3



At the time of the original survey 25% (33 subjects) of the group that did not volunteer to participate in the home treatment and follow-up program were receiving drug therapy for hypertension; 15% of these were under "good control," i.e., average diastolic B P less than 95 mm Hg. The same group was resurveyed in 1966 at the end of the community program and again two years later.

TABLE 4



The "home follow-up" group consisted of 88 subjects who volunteered and persisted in a community treatment program. This program began in 1964 and ended in 1966. From 1966 to 1968 they were again "on their own." The bar graphs indicate the percentage receiving drugs from their private physicians for hypertension, and the light areas the percentage with average diastolic blood pressures less than 95 mm Hg ("good control").

(Continued from Page 1236)

WANTED: Physician for opening in busy established GENERAL PRACTICE in pleasant out-state location. Salary of $35,000.00 1st year. Write MINNESOTA MEDICINE—438, 375 Jackson, St. Paul, Minn. 55101.

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IMMEDIATE OPENING: Internist or General Practitioner to join six man multispecialty group in northeastern Wisconsin. Excellent professional opportunity to practice in a friendly community, only two actively practicing physicians (General Practitioners) in the community outside of our clinic. Salary commensurate with training and experience first year and then full partnership. Ideal, safe small city living for the family on scenic Lake Michigan with excellent fishing, boating and hunting. All this and still only 1½ hours drive to Milwaukee or 45 minutes to Green Bay or lovely Door County. For complete details contact Robert E. Myers, M.D., Garfield at 23rd, Two Rivers, Wisconsin 54241.

Worry

A Chicago physician specializing in research on ulcers told recently that his laboratories had been obliged to abandon the use of dogs in their experiments. The fool critters just wouldn't worry—and worry is the thing that makes ulcers and keeps them active. You can inflict an ulcer upon a dog by artificial methods and he will sit down placidly and cure himself by refusing to be bothered about anything. It's just possible that there might be a lesson here for humans!

Lee Ragsdale

Modifying Elevated Blood Pressure*

A Practical Office Approach

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Minneapolis, Minnesota

IN THE TREATMENT of benign essential hypertension, the first line of therapy consists of the use of the diuretic agents. This group includes the thiazide drugs and chlorthalidone (Hygroton®). It also includes spironolactone (Aldactone®). The thiazides and chlorthalidone are almost identical in action and side effects and can be considered together. These drugs provide very effective antihypertensive action with relatively few side effects. They lower the blood pressure not only in the upright position but also in the recumbent position. Since the diuretic drugs seem to give the smoothest treatment with the least cerebral and postural side effects, they would appear to be our best drugs. We therefore use them in fairly high doses if necessary, on the theory that we should utilize our best drugs to the fullest extent before we add somewhat less satisfactory agents.

There is no great urgency in cases of benign hypertension and we gradually build up the thiazide dosage over a four-to-six-week period. This is relatively important because the thiazide, if given in a large dose all at once, will cause a considerable drop in extracellular fluid volume and cardiac output, which will produce symptoms of faintness and fatigue and may induce the patient to stop taking the drug. However, after a week or 10 days, an adaptation occurs in which the extracellular fluid volume returns almost to normal and the cardiac output becomes normal.

Period of Adaptation

Our strategy is to give a small dose of thiazide the first week and allow adaptation to occur. The second week we increase the dose and allow the patient to adapt to the increment. During the third week the dose is again raised and adaptation allowed to occur. At this point, we can go on to fairly high dosage levels without causing the symptoms of extracellular fluid deficit.

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†Professor, Department of Medicine, Division of Internal Medicine, University of Minnesota Medical School.

As an example of this type of regimen, we would start with 500 mg. a day of chlorothiazide and maintain this dosage for about a week. During the second week we would increase the dose to around 750 mg. a day. Then, during the third week, we would give about 1,000 mg. a day. We might find that the blood pressure had been lowered to an acceptable level with this dosage, and we might not raise the daily ration any further. However, if the blood pressure was not sufficiently reduced, we would then go on to 1,500 mg. a day. We would be able to do this without causing any serious feelings of faintness. In patients with very severe hypertension, particularly those with grade 3 or grade 4 eyegrounds, we might proceed to 2,000 mg. a day of chlorothiazide.

Our maximum dose of hydrochlorothiazide would be 200 mg. a day. When using chlorthalidone, we would consider 200 mg. a day as a maximum dose. With bendroflumethiazide (Naturetin®), we would consider 20 mg. the highest dose. Patients taking these diuretics are asked to restrict somewhat their use of table salt.

Sequellae

Rising Uric Acid

Difficulty is encountered in a small percentage of patients on thiazide drugs; occasionally the rising uric acid level precipitates joint symptoms. But these can usually be controlled with the addition of small doses of probenecid (Benemid®), which will lower the uric acid level to the normal range and eliminate the joint symptoms.

Low Serum Potassium

An occasional patient taking digitalis may suffer from the low serum potassium levels induced by thiazides. In these patients an additional potassium-sparing agent would be added to make the digitalis therapy smooth. We ordinarily use spironolactone for this purpose, but other potassium-sparing drugs, such as triamterene, would also be satisfactory. If a person has diabetes in his family, large doses of a thiazide may precipitate overt diabetes.

In patients with either a high uric acid level or diabetes, we prefer to use spironolactone rather than a thiazide as our base diuretic drug. Although our experience with spironolactone has been limited to only 13 months, we have the strong impression that the drug has an effective antihypertensive action and can exert this action without raising uric acid levels, without precipitating diabetes, and without lowering the serum potassium level. Moreover, it can be used concomitantly with thiazide drugs to keep the potassium level near the normal range.

We give between 50 and 100 mg. of spironolactone daily. When administering this drug, one should remember that it tends to raise the serum potassium level above normal. This is usually of no consequence, but if a patient were to be given spironolactone as well as a potassium supplement, the potassium could rise to a dangerously high level. All patients receiving spironolactone should have their potassium levels checked in the early phases of treatment to make sure that the K level is not above 6 mEq. per L. Occasionally, male patients taking spironolactone will have painful breast nipples. The pain will disappear, however, when the dose is greatly reduced.

As a general rule, we try to lower the diastolic pressure to about 100 mm. Hg. with drug therapy, providing this can be done without many side effects. The diuretics will reduce the blood pressure in at least 75 percent of patients with benign essential hypertension if these drugs are used in a fairly heavy dosage. However, there are still many patients in whom the diuretic agents do not lower the blood pressure enough.

Hypotensive Drugs

Methyldopa and Rauwolfia

If the diuretics alone have not reduced the blood pressure to acceptable levels, we add our second line of drugs to the base therapy of the diuretic drug. Our second line of drugs includes methyldopa (Aldomet®) and the Rauwolfia preparations. Of the two, we prefer to use methyldopa first, given in doses up to 1,500 mg. a day. This drug can cause some drowsiness and may even produce slight confusion in certain patients. These symptoms are bothersome but can be overcome when the dosage is reduced. Eventually a satisfactory level of side effects can be achieved. A Coombs-positive anemia has been produced by methyldopa, but this is rare. Watching the reticulocyte count will alert the physician to the onset of this condition.

Rauwolfia

The addition of Rauwolfia to the diuretics brings a further lowering of blood pressure and may reduce the diastolic pressure to the desired level. In very severe cases of hypertension we have used the diuretics plus fairly full-sized doses of methyldopa plus small additions of Rauwolfia to produce additional drops in blood pressure. But we do not like methyldopa and Rauwolfia as well as the diuretic drugs because of their cerebral effects. Rauwolfia may cause serious depression and has also been associated with peptic ulcer. However, if the dosage is kept fairly low, the cerebral effects are minimal. One advantage of these drugs is that they do not lower blood pressure by producing a marked drop in cardiac output. This is apparent because methyldopa and Rauwolfia lower the blood pressure in the recumbent position as well as in the upright position. Since these agents have more side effects than the diuretic drugs, we tend to use them as a second line of treatment. However, they combine well with the diuretics to give added antihypertensive action. Therefore, in patients with benign essential hypertension who are resistant to treatment, we often use these agents in combination with the diuretic drugs.

Vasomotor Reflex Suppression

In patients with moderately advanced benign essential hypertension, the combination of diuretics and the second line of drugs still may not reduce the blood pressure to satisfactory levels. When this occurs, we resort to our third line of drugs—the agents that act by dilating the veins (capacity vessels). Thus the action of the normal postural vasomotor reflexes is suppressed. When these drugs are having their effect, the veins do not properly constrict when a person assumes an upright posture. Therefore blood pools in the dependent veins and the venous pressure falls considerably. This slows the return of blood to the right side of the heart and causes a drop in cardiac output, the major cause of the fall in blood pressure that is associated with these drugs. Since their antihypertensive action depends primarily on a drop in cardiac output, these agents produce more side effects than the other antihypertensive drugs. This is why we prefer to use them only after the first two lines of defense in combination have proved inadequate. In spite of this disadvantage, these drugs can be very effective and even lifesaving in patients with grade 3 and grade 4 hypertension. Furthermore, if such a patient is receiving methyldopa and Rauwolfia in addition to large doses of diuretics, it may be necessary to give only small amounts of the drugs in this third category in order to reduce the blood pressure to acceptable levels.

Vasodilating Drugs

The drugs in this category—those that act by dilating the veins — include *guanethidine* (Ismelin®), *bethanidine* and the *ganglionic blocking agents*. Of these, the most satisfactory one obtainable in U.S. pharmacies is guanethidine which acts by preventing release of norepinephrine at the sympathetic nerve endings and does not block the parasympathetic system as the ganglionic blockers do. Guanethidine is a powerful antihypertensive drug and can be lifesaving when all else fails. It has certain disadvantages in that it lowers the blood pressure much more in the morning than in the afternoon, may cause severe postural hypotension, as would be expected in drugs that work on the capacity vessels, and can cause distressing diarrhea and rectal urgency. In men, it may prevent ejaculation.

Sympathetic Inhibitors

In England, Canada, Australia and New Zealand, it is possible to buy the drug bethanidine in pharmacies. This agent is somewhat similar to guanethidine and has some advantages over it. Bethanidine acts by inhibiting sympathetic action and does not prevent parasympathetic action. In this respect it is similar to guanethidine. However, it does not seem to produce the diarrhea associated with guanethidine therapy and its length of action is shorter, the effect of a given dose usually lasting about eight hours. Therefore, it is possible to give a larger dose at noon in order to combat the afternoon rise in pressure that is commonly seen with guanethidine. Guanethidine has such a long action that one might as well give the entire daily dose at one time; furthermore, the dose cannot be timed to take care of the afternoon rise in blood pressure. The relatively shorter action of bethanidine allows for an extra-large dose to combat this afternoon rise in pressure.

The ganglionic blocking agents are effective antihypertensive drugs and have saved the lives of many patients with grade 3 and grade 4 hypertension, but they have the disadvantage of paralyzing the parasympathetic nervous system. For this reason, these drugs have been superseded by guanethidine and bethanidine. However, we have used them at times to overcome the diarrhea caused by guanethidine. For instance, the ganglionic blocking drug mecamylamine (Inversine®) is constipating because it paralyzes parasympathetic action of the intestine. If small doses of this drug are given in addition to guanethidine, the diarrhea produced by the guanethidine is often alleviated. (A still better solution would be the use of bethanidine when it becomes available in this country.)

We prefer not to use guanethidine as a first drug but rather to add it to the regimens of patients who are already receiving diuretics and methyldopa. This permits us to use a much smaller dose of guanethidine, with considerably diminished side effects. Used in this way, guanethidine can be a very helpful drug.

Concluding Summary

One of the main ways by which hypertension increases mortality is through its acceleration of the processes of coronary atherosclerosis. Hypertensive subjects, both men and women, definitely have more heart attacks and angina pectoris than comparable normotensive persons. Hypertensive patients must be considered a high-risk group from the standpoint of prospective myocardial infarctions. Therefore, if an effective "anticoronary" regimen of any kind is ever developed, it should be applied to all patients with benign essential hypertension.

The Heart Besieged

True, it is not always possible to find out what subsequently happens to patients. It is not easy to locate a patient five or ten years after an operation and ask him how he is. But information is available about quite a few of them.

A shoemaker operated on by Janelidze returned to his trade and lived as he had lived before he was wounded.

Surgeon Magula's patient was a teamster. Ten years after his operation he hauled loads just as he had done before it.

Some of the patients were even called up for military service.

A stevedore who had had a cardiorraphy complained about a heaviness in the region of the heart whenever he picked up a load weighing more than a hundredweight.

After a cardiorraphy one of Janelidze's patients contracted syphilis. Then he had scurvy, and then typhus and relapsing fever, pneumonia and pleurisy. Finally, he had a bad case of influenza. All this in twelve years. Yet his sutured heart bore it all.

In 1916 Professor Grekov performed a heart operation. Six years later his patient came for a medical check. In the absence of the professor another surgeon examined him. The patient was found to be fit. He had a normal pulse, and normal heart tones. He could easily walk 30 miles and climb to the sixth floor several times a day. Only the scar on the left side of his chest, which receded a bit every time his heart contracted, reminded him of his heart operation.*

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*L. Fridland, M.D.: The Achievement of Soviet Medicine, Edited by W. Horsley Gantt, M.D., 1961.

Cigarette Smoking*

The Associated Cardiovascular Risk

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That tobacco might exert detrimental effects on the cardiovascular apparatus seems not to have been recognized until 50 or 60 years ago when the diagnosis of tobacco angina was popular. Not until 1908 was plausible evidence submitted that cigarette smoking might be implicated in the pathogenesis of the arteriopathy now known as Bürger's disease or thromboangiitis obliterans. It was suggested that this disorder, having some of the characteristics of an acute inflammation, occurred exclusively in young Jewish males who were invariably heavy cigarette smokers. Remissions and exacerbations of the disease were strikingly related to cessation or resumption of cigarette smoking. On the other hand, DeBakey[7] concluded from observations made during World War II on large numbers of young soldiers with this disorder that the role of tobacco is not important. More recently Wessler[21] has asserted that atherosclerosis and thrombo-embolic disease adequately account for the clinical picture recognized as Bürger's disease, while McKusick[15] has vigorously and persuasively rebutted this view, citing typical examples in cigarette-smoking Orientals. How tobacco accounts for the clinical syndrome of thromboangiitis obliterans is completely unknown.

Physiologic Basis of Obliterative Disease

Cigarette smoking is generally conceded to have an adverse effect in the common variety of obliterative peripheral vascular disease. The physiological basis for this effect is well established. While muscle blood flow, as measured by the clearance of injected radiosodium, is little changed by cigarette smoking, there is a sharp curtailment of skin blood flow, measured by temperature change or by plethysmograph. Where arterial inflow is compromised, such a critical reduction in skin blood flow predisposes to ischemic ulceration which accounts for most of the disastrous complications of obstructive peripheral arterial disease. The measurable circulatory effects of smoking are attributed exclusively to the amount and rate of nicotine absorption and are acute, transient and noncumulative. Sham smoking and the smoking of denicotinized and non-tobacco cigarettes fail to produce any circulatory changes. Nicotine powerfully mobilizes catecholamines, particularly epinephrine. As a consequence, there are modest increases in heart rate, cardiac output and stroke volume and arterial blood pressure lasting 15 or 20 minutes. The effect of tobacco smoke on coronary blood flow in humans is incompletely known. In most instances consonant with the rise in arterial blood pressure and in cardiac output there is an increase in coronary blood flow. There is some evidence that blood flow may not increase in coronary obstructive disease in proportion to the rise in heart rate and in blood pressure, i.e., the time-tension index, which primarily determines myocardial oxygen consumption.

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*Presented at the Minnesota Symposium on Prevention in Cardiology, May 2-3, 1968 in Rochester, Minnesota.

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Sudden Death and Myocardial Infarction

The unfavorable influence of cigarette smoking on certain types of heart disease has been recognized only fairly recently. Incidental to the large retrospective studies of the relationship between cigarette smoking and lung cancer undertaken about 15 years ago a large excess of deaths from coronary heart disease was observed in cigarette smokers. At about this time the prospective studies of cardiovascular degeneration in Framingham, Massachusetts, and in Albany had accumulated several years' experience.[10,11] The prevalence and the preliminary incidence data showed a consistent but not statistically significant association between ischemic heart disease and the tobacco habit.

Mortality

Pooled observations were able to show a significantly larger number of cases (approaching 200%) of sudden death and of acute myocardial infarction in men smoking 20 or more cigarettes daily, compared with non-smokers. There appeared to be a gradient of risk related to the number of cigarettes smoked but not to the duration of smoking. In one million men and women Cuyler Hammond[12] has shown a mortality ratio in the 45- to 54-year-old range of 2.81 in male smokers compared with non-smokers, and in women of 2.00.

Epidemiological studies have shown a statistically significant relationship between the smoking of 10 or more cigarettes daily and the occurrence of acute myocardial infarction and sudden death. No specificity of this relationship has yet been shown. The reason for the pernicious effects of cigarette smoking continues to defy explanation.

Morbidity

Compared with non-smokers, men smoking 60 cigarettes daily had a morbidity ratio as high as three while men smoking fewer cigarettes had a lower rate. Furthermore, there appeared to be a decline towards the morbidity experience of non-smokers in men who gave up cigarette smoking. Pipe and cigar smokers had about the same experience of myocardial infarction as non-smokers. Finally, no relationship could be demonstrated between cigarette smoking and angina pectoris as a solitary clinical manifestation of coronary heart disease. The evidence which has accumulated in these two studies since the first report on smoking has reenforced the initial observations. Other prospective studies have been, in general, confirmatory.

Seltzer[18] has indicated that inversions and anomalies can be found in the newer data. In particular, the morbidity experience of ex-smokers is not so favorable as originally appeared, although the health status and the motivations of people giving up smoking may well be different now from some years ago. Retrospective pathologic studies have shown good correlation between the severity of coronary atherosclerosis and the number of cigarettes smoked.

Physical Fitness

Although cigarette smoking is condemned by athletic coaches, there is remarkably little evidence showing impaired physical fitness in cigarette smokers. Cooper[6] has, however, recently shown that during basic military training, heavy smokers have less endurance than non-smokers, although athletic training and ability are also important factors.

The possible interrelationships of cigarette smoking with other risk factors have been intensively scrutinized. While catecholamines mobilize free fatty acids, there is no evidence that the triglyceride or cholesterol concentrations in the serum of smokers differ from those of non-smokers. Body weight is not a factor. Indeed, smokers tend to be somewhat lighter than non-smokers. There is no correlation between the smoking habit and arterial blood pressure, although hypertension notoriously accelerates and exacerbates coronary heart disease. If anything, smokers tend to have lower blood pressure levels than non-smokers.

Much attention has been directed to the influence of cigarette smoking on clotting mechanisms,[16] on the Rokitansky-Duguid thesis that thrombosis initiates atheropoiesis and is certainly responsible for the ultimate catastrophic complication of occlusion at the site of atheromatous ulceration. In-vitro methods of measuring clotting are crude and unreproducible in the extreme. Probably the most suggestive evidence is that platelet turnover and platelet adhesiveness seem to be increased by cigarette smoking, and hence may favor the formation of an arterial clot. On the other hand, it is well known that obstructing clots are scarcely ever found in cases of sudden death despite the invariable presence of widespread atherosclerosis, and begin to appear with regularity only 24 hours or so after the initial catastrophe. Very recently it has been observed that in dogs exposed to cigarette smoke the threshold for ventricular fibrillation becomes subnormal for periods up to an hour.[20] If this is indeed true, it provides a convincing explanation for the high frequency of sudden death in heavy smokers. The apparent difference in reactivity of patients with angina pectoris remains puzzling. Finally, it should be emphasized that the risk of cigarette smoking becomes much attenuated after the age of 55.

Conclusions

There is convincing circumstantial evidence that heavy cigarette smokers prior to the age of 55 have a substantially higher rate of myocardial infarction and of sudden death than non-smokers, both men and women. Cessation of smoking appears to be rewarded by a reduction in risk of myocardial infarction and sudden death. The heavy cigarette smoker is, of course, also subject to chronic bronchitis and to pulmonary emphysema. Both are causes of cor pulmonale, which is a most serious complication not only of coronary but of any type of heart disease. Despite the lack of explanation for the lethal effect of smoking, there is ample evidence to justify discouraging the young from acquiring the habit, persuading the adult to abandon the practice, and to forbid, unequivocally, smoking by the victim of cardiopulmonary disease. Immoderate cigarette smoking is a special form of self-induced atmospheric pollution and as such constitutes one of the major challenges now confronting public health.

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Ours is a world of nuclear giants and ethical infants.—Omar Bradley

|| Smoking*

Reducing the Dangers

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Of the ten leading causes of death, smoking has been associated with eight of them. The ninth may well be included, if you consider the man who drives through the guardrail while trying to light his cigarette. A medical index[1] lists over one hundred diseases that are related to cigarette smoking.

The association of the cigarette habit with so many separate diseases is an indication of the complex composition of cigarette smoke. If the cigarette emitted only one noxious agent, it might be possible to identify and render this agent innocuous. The cigarette, however, emits hundreds of noxious agents, each producing its own pathophysiological effect.

Carcinogenesis

You will frequently hear from public relations sources close to the Tobacco Industry, that the association between cancer of the lung and smoking is only statistical, has not been proven, and that much more research is needed. Except for the confusion that is intentionally instilled in the public's mind, it would be hard to disagree with some of the elements of this statement.

At least thirty of the substances within the smoke either are carcinogenic or promote carcinogenesis. The components that are known to be carcinogenic are, for the most part, aromatic hydrocarbons; but these hydrocarbons represent only a small fraction of the total carcinogenic properties of crude tar derived from cigarette smoke. While there can be no reasonable doubt that cigarette smoke has a casual relationship to lung cancer, a great deal must yet be learned as to how it initiates the malignant changes.

In evaluating carcinogenesis we do have a satisfactory assay system: something not yet available in cardiovascular research. Many investigators attempted to produce lung cancer in a variety of animals and, until recently,[2] these experiments failed, largely due to the lack of cooperation by the animal involved. It is yet to be determined whether the animal's reluctance to inhale smoke is an act of brilliance or stupidity. In any event, the technical aspects of producing lung cancer were so great that it seemed desirable to develop another means of evaluating the carcinogenic properties of tobacco tar. Wynder,[3] in 1953, was able to report the first extensive production of skin cancer in mice by application of cigarette smoke condensate. Subsequently, it was observed that cigarette tars could produce tumors in a variety of animals, such as hamsters, rabbits, rats and fowls.

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Convenience and economic factors ultimately decided in favor of the mouse for use in a carcinogenic assay system. Cigarette smoking machines were designed that could smoke as many as 20,000 cigarettes per day, and the tars extracted from the smoke could then be analyzed and used in biological experiments. Extraction of tars from cigarettes and the production of malignant tumors in mice by application of the tars to the skin has become a high-school biology experiment. One cannot, without reservation, apply to the human population, data obtained from experimental models that use mice; however, the more the mouse skin assay system was used, the more it seemed to correlate with human experience. For example, it has been established that the incidence of lung cancer in Scotland, England and Wales is nearly twice that of the United States. Tars extracted from English cigarettes and used in the mouse skin assay system were found to have nearly double the carcinogenic properties of the tar extracted from American cigarettes.[4]

Hazards Identified through Mouse Skin Assay

Some of the factors that make the English cigarettes so hazardous become more apparent as information becomes available through the mouse skin assay system. Ten years of experience in the use of this system now allows us to make the following general statements:

1. Daily application of the tar from about eight cigarettes causes the development of precancerous and cancerous skin lesions in mice[5] in less than one year.

2. The number of tumors and the time of development depend upon the amount of exposure to the tar. For example, repeated daily application of 50 milligrams of tar will produce approximately twice as many tumors as 25 milligrams of tar.[6]

3. Equal amounts of tar will produce tumors at variable rates, depending on the type of vegetable leaf used to obtain the tar. For example, tar from cabbage is more carcinogenic than tar from Virginia tobacco, which in turn is more carcinogenic than tar from Burley tobacco, lettuce or maple leaves.[7]

4. Flue-cured tobacco is considerably more carcinogenic than air-cured leaf.[8]

5. The carcinogenic properties of the whole tobacco tar are about two hundred times greater than the sum of the carcinogenic properties of all the known carcinogens within the tar.[9]

6. There are agents in the raw tobacco leaf, in all probability present during the combustion of cured tobacco leaf, which can promote and accelerate carcinogenesis, but which, of themselves, are not carcinogenic. Many of these agents are yet to be identified and their modes of action described.[10]

7. The known carcinogenic properties of cigarette smoke are found primarily in the particulate phase; however, substances within the volatile fractions of the smoke may well compromise the lung's ability to protect itself from harmful agents.[11,12]

8. Substantially more carcinogenic tar is delivered to the smoker if the cigarette is smoked to a very short butt (23 mm.).[13]

9. Filters vary considerably in their capacity to remove carcinogens from cigarette smoke. Effective filters are rarely found in the most popular brands of cigarettes.[14]

The Most Carcinogenic Cigarette

If it were one's intent, through knowledge presently available, to develop the most carcinogenic cigarette possible, one would incorporate in its design the following features: select a flue-cured Virginia tobacco, cut it very fine and pack it tightly into a cigarette with a paper overwrap of low porosity. (Decreased paper porosity provides for slower burning and higher temperatures, and permits a significant number of extra puffs.) Filters should not be used, or if so, one of those that are practically ineffective. Further, the user of this most hazardous cigarette should be allowed to smoke it to the shortest butt possible. The description and use of this hazardous cigarette is not unlike the manufacturing design of current English brands, or the smoking habits of the people who use them.

Cardiovascular Disease

There is, also, no reasonable doubt that smoking is related to coronary heart disease, but there are many questions yet unanswered as to how it is related. While we seek to understand the association of aromatic hydrocarbons, polonium, terpenes, crotamines, phenols, and the nitrosamines to lung cancer, we must also consider what there is in cigarette smoke that makes the platelets stickier, or alters the coagulability of the blood, or causes myocardial anoxia, or elevates the serum cholesterol and lipids. I feel confident that the cause of smoking-related heart and circulatory diseases will prove to be far more than a simple nicotine or carbon monoxide effect.

There is much that remains to be done to identify and nullify the agents in smoke that affect the cardiovascular system, but we can start by removing carbon monoxide and nicotine.

Carbon Monoxide

Carbon monoxide's great affinity for hemoglobin displaces oxygen and probably aggravates a nicotine-created myocardial anoxia. Carbon monoxide can be selectively filtered out of the gaseous phase of the smoke.

Nicotine

Nicotine, a lethal agent, which has well recognized and measurable physiological effects, can be reduced or removed by a number of techniques. Nicotine can be extracted from the leaf or filtered from the particulate phase of cigarette smoke. Selecting small leaves from the top of the tobacco plant and modifications of the curing process will also reduce nicotine. Unfortunately, when you remove nicotine from a cigarette, it deprives the smoker of an element that he craves. The most popular brands of cigarettes are those with the highest tar and nicotine ratings.

Other Vegetable Smoke Toxicity

Different forms of vegetable matter have widely variable combustion characteristics. In order to evaluate these variables, we established our own farm just outside of Buffalo, where we have grown the most commonly used types of tobacco. We have manufactured our own cigarettes, using blends of tobacco, as well as cabbage, lettuce, catalpa, petunia and sugar beet leaves. These cigarettes were then placed in the smoking machine described earlier and the tars extracted from the smoke applied to the skin of mice. Equal amounts of tar will produce tumors at variable rates, depending on the type of vegetable leaf used to obtain the tar. For example, tar from cabbage is more carcinogenic than tar from Virginia tobacco, which in turn is more carcinogenic than tar from Burley tobacco, lettuce or maple leaves.[7] I should hasten to point out that while our competitors advertise their cigarettes to be like Spring, ours are, unfortunately, more like Fall on a wet day.

The Tar Content

The longer the cigarette is, the greater the yield of tar. The further down you smoke the cigarette, the more hazardous it becomes. The 7 mm. just in front of the filter yields the greatest amount of tar per puff. In view of this, the development and distribution of an unfiltered 100 mm. cigarette is the height of irresponsibility.

The person who smokes less than a half pack of cigarettes a day has little to fear from an increased risk of either cancer or coronary heart disease. Cigarettes can be designed so as to allow an individual to smoke a pack or a pack and a half, but at the same time deliver the harmful effects equivalent to that of only half a pack per day.

Tar content of the smoke per cigarette can be reduced by wrapping the cigarette with aluminum foil to the half-way point so that it will not burn beyond that point. It is also possible to chemically treat either the cigarette paper or the tobacco in such a way as to alter the combustion characteristics so that a greater residue is produced in the ash and fewer chemicals are present in the smoke. Care must, of course, be exercised not to add something that is more noxious than that which is removed.

The Space Age Cigarette

The Tobacco Industry has responded to the public concern about the hazards of smoking by flooding the market with a series of gimmicks, about which it is never stated, but always implied, that this or that makes their particular brand safe or a little safer. The Figure shows what a future cigarette might look like if all the gimmicks were placed in one brand. Since tobacco is known to be hazardous, there should be very little tobacco in this cigarette, probably enough to light and inhale once, but behind the tobacco there must be something, perhaps lettuce.

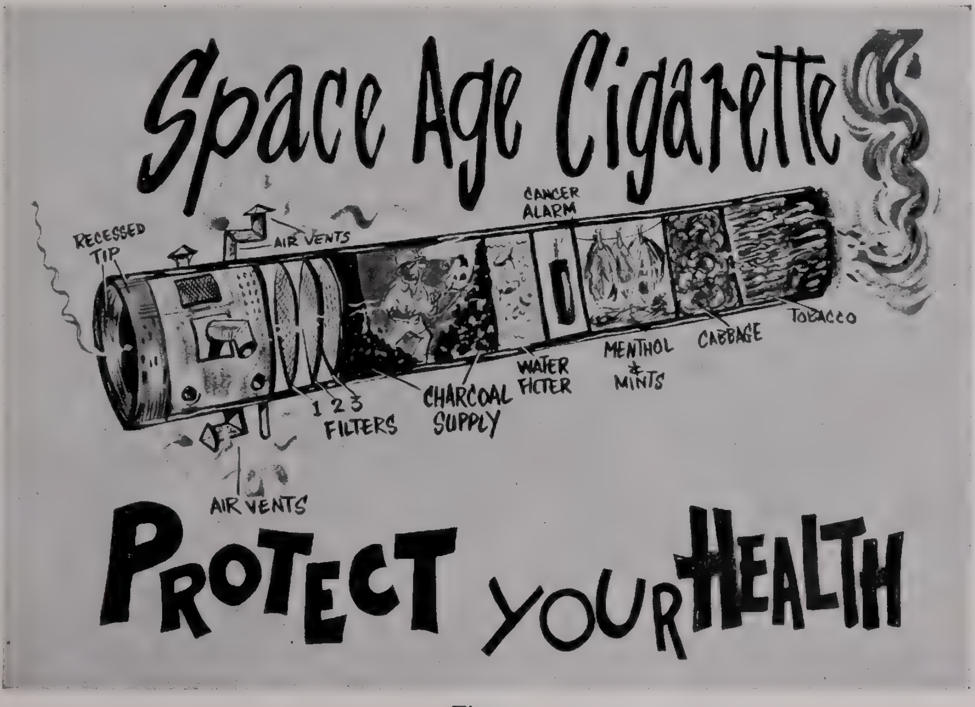
When all the pathological processes are finally identified, it may be possible to selectively remove the offending agents from the smoke. Doubtless, with the extraction or neutralization of the harmful ingredients, some of the "pleasurable aspects" of smoking might disappear, but conceivably some of them could be restored by lacing the cigarette with exotic, but innocuous, additives.

Since we are depriving the person of many of the things he craves, there should be a liberal amount of spices, mints or menthols to convince him that he is getting something. The further down he smokes the cigarette, the more hazardous it becomes; therefore some sort of an alarm system should be built in at the half-way point. The water filter, or the principle of the Turkish Hooka, is quite effective, but we never thought we would see it in an American cigarette.

However, not long ago, one brand was marketed with pellets in the filter, which if squeezed, allegedly would inundate the filter with water. There should be a liberal amount of activated charcoal, along with several filters of the cellulose type or other synthetic types now being developed. Preferably there should be air vents in the side. Obviously, if you inhale from the cigarette that has air vents in the side, you are going to get a large draft of air and very little smoke. Last is a recessed tip. To be perfectly frank with you, I don't know what this does, but whatever it is, it keeps you a quarter of an inch away from it.

Concluding Comments

It should not be implied that a significant margin of safety has been found that will



Figure

allow people to smoke cigarettes with impunity. There is some evidence that as high as our smoking-related cardiovascular disease and lung cancer rates are now, they are not as high as they would have been had we not started to use filtered cigarettes in 1955.[15] There will be no easy solutions to these far-reaching health problems, but we should seek to find means of dissuading the young from starting the cigarette habit and to encourage the adult who cannot stop to at least ease off until some more answers can be found that will provide greater protection. The cigarette can and should be redesigned, preferably voluntarily, but by legislation if necessary, to make use of the scientific data currently available. The known hazards and noxious contents of cigarettes should be clearly labeled on the pack and in all cigarette advertisements. Because of the hundreds and thousands who will suffer disability and premature death, we must continue to try to discover the exact means by which cigarettes induce disease processes and make sure that this knowledge is used as effectively and as rapidly as possible.

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Heart Dignostics in Ancient Egypt

When dryness befalls his Heart, behold it is the dryness of Fire that befalls it. He sighs often and his Heart is eaten up with anger; this is because his Heart is full of Blood, which in turn is due to drinking Warm Water and eating Bad Food.

When his Heart is afflicted and has tasted sadness, behold his Heart is closed in and darkness is in his body because of anger which is eating up his Heart.

When it is Fate that he shall go Up-on-High, behold it is his Heart which determines that he shall go Up-on-High.*

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*Bryan, Cyril: The Papyrus Ebers, D. Appleton and Company, New York, 1931, p. 126-131.

By the street of "By and By" one arrives at the house of "Never."—Cervantes

Help Your Patient Stop Smoking

Guidelines for the Office Physician[*]

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THE OVERWHELMING WEIGHT of scientific evidence clearly establishes cigarette smoking as a grave threat to personal health. As physicians we forfeit an unparalleled opportunity to practice highly effective preventive medicine when we fail to warn patients and, in particular, younger patients, on the dangers of smoking. Yet recent evidence[1][‡] indicates that many physicians are not fully meeting their responsibilities on this critical health issue. In part, some of the hesitancy to speak firmly to patients about smoking may reflect an inadequate acquaintance with the evidence linking cigarettes to human disease and the benefits to be gained by quitting. I believe a far more significant fact is the physician's uncertainty as to how to approach the patient who wants to stop smoking and how to deal effectively with that inevitable inquiry: "O.K. Doctor, I believe what you say about smoking, now how do I go about stopping?" It is my intention to grapple with this and other questions related to smoking withdrawal and present a guideline that may be useful to the practicing physician in assisting his patients to stop smoking.

To be effective the physician must know where he stands on the cigarette controversy. He must be certain of his facts and formulate a clear position regarding his patient's smoking behavior. A vague, poorly defined idea that smoking is deleterious to health and somehow related to cancer will not do. For, once the cigarette issue has been raised, the patient will press with numerous questions and will expect forthright and intelligent answers. With only a hazy understanding of the relationship of smoking to cancer, respiratory disease and the cardiovascular diseases, the physician may feel uncomfortable in dealing with these and related questions. Half-hearted, watered-down instructions to stop smoking may be worse than no instructions at all. Smokers frequently search for excuses to continue smoking and may interpret uncertainty on the part of the doctor as an indication of his lack of interest or concern and an implied endorsement to continue smoking.

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Presented at the Minnesota Symposium on Prevention in Cardiology, May 2-3, 1968 in Rochester, Minnesota.

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[‡] In a recent national survey of physicians the overwhelming majority (77%) of the doctors polled agreed with the statement: "It is the physician's responsibility to attempt to convince his patients to stop smoking." An even larger proportion (86%) agreed that if a patient wants to stop smoking, it is the physician's responsibility to help him accomplish this. And yet only 38% of physicians said that they advise all or almost all of their patients who do not have any condition related to smoking to quit or to cut down.

The Public Health Service has produced an excellent summary of the 1964 Surgeon General's report[2] and has recently[3,4] updated this. In addition they have available for distribution at least six pamphlets[5] for lay consumption that persuasively argue the case against the cigarette.

Motivating the Smoker

Debilitating Chronic Disease

While it is certainly legitimate to make reference to increased death rates and elevated risks of developing cancer, the idea that by quitting smoking you significantly lower the odds of *early disability* (in the 40's and 50's) has a special meaning, particularly for the young smoker with a growing family and enlarging professional and community responsibilities. Many smokers say: "Dying doesn't bother me—after all you've got to die of something. And I calculate my chances of developing lung cancer to be relatively small." However, the idea of spending 15 or 20 years with debilitating chronic disease that interferes with the enjoyment of life and reduces ability to function is another matter. This shift of emphasis will frequently shake the young smoker out of his lethargy to the point where, for the first time, he may honestly confront himself with the thought: "Here is a problem that I have a responsibility for doing something about!"

Improving Health

Another point to emphasize is that irrespective of how long or how much one has smoked, there is everything to gain by stopping. A man with a 30-year habit may rationalize his smoking by saying: "The damage is already done—no reason to stop now!" Many intelligent people who have been smoking for many years respond with great surprise to the knowledge that if they stop, the injury associated with the smoking also stops and, because of the body's amazing recuperative powers, a significant amount of damaged tissue may be replaced or repaired.

Upper Respiratory Symptoms

It is worth discussing with all patients the *immediate* effect of smoking on the body. If an individual can begin to appreciate that each drag on his cigarette is something of a body blow to his delicate biological mechanisms, smoking may take on a heightened sense of personal relevance. Here two approaches suggest themselves. The physician can make a direct connection between the smoker's cigarettes and his symptoms — cough, morning phlegm, draining sinuses, shortness of breath, mid-day fatigue. Respiratory symptoms in particular can be legitimately and effectively tied to the cigarette habit. The physician can also give a brief description of the action of cigarette smoke on the mucociliary apparatus, stressing the importance of the cilia as the principal cleansing mechanism of the respiratory tree. The knowledge that each cigarette puff works to paralyze this delicate system will impress many smokers. The patient may then begin suggesting to himself: "Just taking this one cigarette does actual physical harm to my body."

Props

There are ways that the subject of smoking can be introduced effectively without disrupting a busy office routine. Indeed, the ability to wage psychological warfare against the cigarette habit should be limited only by the imagination and ingenuity of the doctor and his staff. Pamphlets, posters, and table-top displays may be secured from the Public Health Service or local voluntary health organizations. Ash trays should be conspicuous by their absence from the waiting room. A detailed review of smoking behavior can be incorporated into the history form—its very presence suggesting its importance to the doctor. As an example of innovative health education one physician of my acquaintance has his office nurse hand each patient a pamphlet on smoking while sitting undressed waiting for the doctor's examination. On leaving the room she remarks: "I suggest you read this; the doctor usually asks his patients about its contents." Another physician reserves his most pointed questions about smoking for the examination of the chest. As he stands behind the patient listening through his stethoscope he inquires in a serious vein: "How much did you say you smoke? For how long? Cough again, please!"

Retraining the Smoker

Learn To Be a Non-smoker

The patient should be given a rational explanation of what he must do if he is to succeed in breaking the habit. He can be told that as far as we know cigarette smoking is not a physiological addiction; rather it is a psychological addiction built upon a habit. A habit is nothing more or less than a form of *learned* behavior. If one can learn to be a smoker one can reverse the process and learn to be a non-smoker. For the discouraged and defeated smoker the idea that one can relearn or retrain oneself to be a non-smoker helps establish self confidence. No matter how downhearted the smoker may be, he is told that because he never loses the capacity to grow and learn new, more constructive, and healthier ways to behave, he never loses the ability to transform himself into a permanent non-smoker.

Motivation

Learning to be a non-smoker requires that the individual must first generate motivation. Health is the most compelling reason to stop but is by no means the only one. For example, some people stop because they are annoyed at having lost control of their habit. Others will stop not for themselves but for their family or as a positive influence for their children. Others stop for esthetic reasons; they consider the habit dirty or otherwise personally offensive. For some the economics of smoking may have significance; a 30-year habit at 5 percent compound interest adds up! And there are those who will stop in response to a challenge: they will stop on a bet! The physician should be sensitive to these incentives and appreciate that what motivates one smoker may not work for another. In counseling the patient all avenues should be explored.

The second task is to begin changing smoking behavior: the area where the physician offers his most specific guidelines. Here is the training program used in our withdrawal clinics:

The Smoking Record

The patient is instructed to wrap his pack of cigarettes in a piece of 8½-×-11 inch paper and secure this with rubber bands. He may smoke ad libitum for the next two weeks. However for *each* cigarette smoked he must complete the following procedure: unwrap the pack and note the following on the paper: a) time of day; b) the activity he is engaged in while smoking (e.g., working, answering telephone, drinking coffee or cocktails, etc.); c) his emotional state while smoking that cigarette (e.g., bored, angry, tense, nervous, etc.). He then assigns a value to the cigarette on a rating scale: I, II, III, IV, V. Each cigarette is measured against all others smoked during the day. If it is one of the most important, one that he cannot do without, it is rated I. On the other hand, if it is one of the least important, one that he could take or leave, it is rated V. All others fall somewhere in between with each succeeding category containing cigarettes of lesser importance than those in the preceding one.

This simple almost humorous instruction is one of the most powerful psychological weapons at the smoker's disposal. It should be seriously given by the physician. The patient is told that no exceptions can be made—that every cigarette is to be noted. If for some reason he feels he can't record a particular cigarette it is not to be smoked. If he "bums" or takes a puff from someone else's cigarette this is noted on the record.

The wrapping procedure is the critical first step in the withdrawal process. No further explanations are given. There are no specific instructions to reduce smoking. The patient is asked to return in one to two weeks.

On the second visit the record is collected and the patient asked to tell what he has learned about himself and his smoking. Smokers usually relate the following: (1) that simply by keeping the record he has begun to reduce his smoking. The first cigarettes to go are the III's, IV's and V's. (2) All cigarettes are not alike; they have different meanings and are used for different reasons: this is the beginning of insight into why he smokes. (3) Part of smoking is automatic, almost subconscious; there are certain cigarettes that he lights with very little awareness of what he is doing. (4) There are strong associations between cigarettes and specific activities (coffee, cocktails, after meals, etc.) as well as with certain feeling states (anger, tension, boredom, sense of well being, etc.). (5) There are but a handful of cigarettes that he really enjoys. Even heavy smokers will frequently report only three or four cigarettes in a day's consumption that are truly important.

Additional Instructions

a). Establish a pledge card. On this indicate a target date for complete cessation. Each morning pledge how many cigarettes will be smoked that day. At the end of the day record the performance, i.e., the extent to which there was success in meeting the pledge. Plan the reduction so as to be down to four or five cigarettes by the target date for stopping.

b). Develop a list of reasons for wanting to stop. Review this several times a day. Reduce it to the two or three most important reasons. In building the list we suggest concentrating heavily on the *positive* benefits of stopping.

c). Buy only one pack of cigarettes at a time. Never buy a carton.

d). Never carry cigarettes on your person. At work give them to your secretary or put them in another room. At home hide them in the cellar, the attic or the mail box.

e). Never carry matches or a lighter.

f). Hide the ash trays or fill them with cigarette substitutes, i.e., pieces of non-caloric candy.

g). Stock up on temporary substitutes—gum, low calorie candies, artificial cigarettes, etc.

h). Change brands once a week. With each change move to a lower tar and nicotine cigarette.

These instructions provide specific, concrete guidelines which support the smoker as he initiates the process of establishing new habit patterns. The list of reasons assists in focusing on motivational material. The pledge card with its target date for cessation centers the smoker's attention on a goal and provides a visual picture of his progress. The remaining instructions serve as "roadblocks" making it increasingly difficult to obtain each cigarette. This effectively interferes with the automatic aspects of smoking, making each cigarette a painfully conscious act, and provides considerable support in overcoming the urge to take those cigarettes of lesser importance. Again I would emphasize that the manner in which the physician delivers his instructions will, in large measure, determine the degree to which they are given credence and acted upon. If the physician outlines his therapeutic regime as a casual off-hand "well I don't know—why don't you try this," he will forego an opportunity to validate his therapy in the mind of the patient. If, on the other hand, he gives the instructions with an air of authority, saying in effect: "This is what you must do if you are to succeed," he will establish in the mind of the patient his belief in the *method* as well as his skill as a therapist.

Reinforce Attitude

Next to building incentive and altering behavior patterns, possibly the most important task facing the patient is to adopt an attitude that reinforces the withdrawal effort. Basically there are two attitudes the smoker can opt for. He can look upon withdrawal as a minus—an act of denial—a taking away. When he views smoking cessation in this way there is a tendency to self-pity. The longer the denial the greater the psychological distress which, in turn, often generates an intense desire to smoke. Eventually the patient gives in. Frantically lighting his first cigarette he loudly proclaims: "No one should suffer as I have," an attitude all too frequently adopted by smokers in withdrawal. It is powerfully self-defeating. The alternative is to look upon withdrawal as a *plus* in one's life. In stopping smoking you are teaching yourself a new, a more constructive, a healthier, and a more self-fulfilling way to behave. You are building into your personality a dimension of self-control and self-mastery formerly not there. From this will come a heightened sense of self-esteem.

Identifying and discussing these opposing attitudes can be helpful to the smoker and may initiate a switch from one to the other. When the attitude does change, the results are often dramatic. The smoker now looks at stopping as an exciting experiment in self-growth which may literally put a "new face" on the withdrawal program. In this context it is worth noting that the self-confidence that comes from conquering the cigarette habit may spill over into other areas of the smoker's life. When this happens he will experience an increased capacity to deal more effectively with other problems: weight control, alcoholism, work problems, etc. This we call the *ripple* effect—a substantial fringe benefit when it occurs.

Questions Smokers Ask

Once the physician has raised the subject of smoking he often finds that he has opened a floodgate, if not a Pandora's box, of questions. These inquiries must not be brushed aside nor dismissed out of hand. Responses should be formulated that are consistent with current knowledge and that will encourage and reinforce the smoker's efforts. The following are offered as examples of the kinds of questions posed and the responses that might be considered acceptable to both doctor and patient:

Question: Should I stop suddenly?

Answer: Every smoker must eventually stop completely. But why the rush? After all you didn't get into this overnight and I see no reason why you must try to get out overnight. I would suggest gradual withdrawal. This will give you small successes which will restore confidence in your ability to manage the problem. In addition, gradual withdrawal will prepare you psychologically for the time when you are ready to make a bona fide decision to stop completely.

Note: It should be kept in mind that certain types of smokers, possibly those rating high on the Tomkins-Horn "Addictive" scale[6] may have to break the habit suddenly and completely. It is my impression that it is best to let the smoker make this decision. If he feels he cannot taper off, chances are he knows what he's talking about.

Question: Why do I get so nervous when I try to stop? How long will the craving to smoke last?

Answer: Many smokers use cigarettes as they would use a stimulant or tranquilizer—to pick themselves up ("turn themselves on") or calm themselves down ("turn themselves off"), i. e., to modulate a feeling or mood state. When you suddenly take cigarettes away these feelings must be managed without benefit of the smoking "drug." This may result in a temporary though an unusually heavy load of tension and anxiety. For instance, if the smoker has come to rely upon cigarettes to 'pick himself up,' i.e., to accentuate pleasurable feelings (e.g., smoking after meals, with cocktails, during pleasant conversations, while relaxed and feeling good), he must now learn how to find enjoyment in pleasurable situations without smoking. If on the other hand he has come to rely on cigarettes to tone down uncomfortable feelings (tension, anxiety, boredom, fear, rage, hostility, etc.) he will, possibly for the first time in years, have to manage these feeling full force without the benefit of his tranquilizer. In this respect for a short period, he is very much like a steam boiler whose escape valve has been suddenly closed off. To my knowledge no ex-smoker has ever exploded!

The patient is counselled that both the nervousness and the craving are temporary and with time, measured in weeks and for an unfortunate few in months, will begin to subside. The reduction in the nervousness and craving will be the signal that retraining is taking place. It is important to stress that the acute discomfort is short-lived for the great majority of smokers. Otherwise the patient may assume that his distress will last indefinitely and conclude that this is simply too high a price to pay for stopping.

Question: What about the physical symptoms I experience when I try to stop? What causes these? Are they dangerous? How long will they last?

Answer: Smokers frequently report various physical symptoms during and immediately following withdrawal. Certain symptoms (e.g., increased cough and phlegm) may actually reflect the healing process at work. However, most appear to be physical manifestations of anxiety and tension. Examples are: shortness of breath, light-headedness, tightness in the chest, visual disturbances, sweats, headaches, gastrointestinal complaints, etc. The smoker is cautioned not to be alarmed and to look upon his symptoms as an indication that his body is actively readjusting to the non-smoking state. Our experience indicates that symptoms begin to subside within a matter of days or weeks.

Question: What can I do to avoid gaining weight?

Answer: This question is invariably asked. There is a real and for some a powerful drive to overeat during withdrawal. This may reflect a heightened sense of taste and smell and/or the lifting of a toxic effect of smoke on the gastrointestinal tract. However, it is our impression that for the most part overeating represents a substitute for cigarettes. For some the act of eating is a highly effective means of modulating psychological distress. For the occasional smoker there may be virtually a complete substitution of food for smoking, resulting in compulsive overeating and marked obesity. When this occurs I have no hesitancy to point out that the patient is really a "fraudulent" ex-smoker. He has not changed in any appreciable sense, merely switched from one mood-modifying agent to another.

There appear to be no easy answers to the weight gain problem. We advise concentrating on one habit at a time. For the moment forget weight gain. Most successful ex-smokers we have followed find that once the acute craving to smoke subsides they can bring their weight back to normal with a minimum effort. The physician should be alert to the misconception that weight gain is as harmful as smoking and if one has to choose one might as well choose to smoke. We tell our patients that to equal the harmful effects of smoking one pack of cigarettes a day one has to be grossly obese, possibly as much as 80 to 90 pounds overweight—a considerable distance from the ten to fifteen pounds gained by some smokers.

For those who will not tolerate any weight gain we suggest reducing diets. It is our experience that emphasis is best placed on alerting the patient to high caloric foods, particularly high-calorie snack foods, rather then attempting to markedly reduce the number of feedings. If eating gives relief during withdrawal it seems wise to interfere as little as possible with the act itself and concentrate attention on what goes into the mouth, selecting pacifying foods that are low in caloric content.

Question: What about hypnosis? Will it help me?

Answer: To my knowledge there have been no controlled studies with long-term follow-ups on the effects of hypnosis on smoking withdrawal though there are encouraging reports from some quarters. Consequently the best response to this query is: no one knows. One way to find out is to give it a try. If you are going to experiment with hypnosis, however, select a responsible professional who knows what he is about and what his limitations are.

Question: Are there anti-smoking drugs that will help? What about the preparations one can buy without prescription?

Answer: Three classes of drugs have been used to assist smokers during withdrawal: those which simulate the effects of nicotine (primarily lobeline compounds), those which affect the taste sensations of smoking (spicy lozenges, silver nitrate preparations, etc.), and those which modify symptoms attendant on withdrawal (stimulants, tranquilizers, and sedatives). Several well controlled studies have failed to show these preparations to be any more effective than placebos and, while there have been a few scattered reports to the contrary, there is at present no solid evidence to contradict the conclusion of the Surgeon General's 1964 report (page 354): "There is no acceptable evidence that this goal (stopping smoking) can be achieved solely by modifying sensory drives or using tobacco substitutes." Nevertheless it should be borne in mind that many smokers will respond to the placebo effect of taking anything that looks like "medication" and, when detected or suspected, the physician may wish to maximize this advantage by prescribing an inert or mild preparation in a persuasive looking form.

Question: Do you recommend switching to cigars or a pipe?

Answer: It is now clear that the risks of smoking are dose-related. Consequently anything that reduces the dose of inhaled smoke is a step in the right direction. Pipe and cigar smoke is usually not inhaled and therefore less hazardous than cigarettes. I have little hesistancy in sanctioning the transfer if the smoker feels he must have a substitute or considers the switch a necessary move toward complete cessation. It is my impression that heavy cigarette smokers who substitute cigars or a pipe stay with these for only a short period and then stop completely or revert to the cigarette habit. The patient should be cautioned that if he makes the switch and continues to inhale he is certainly no better off. It should also be noted that if the smoker suffers from peripheral vascular disease, switching to a pipe or cigar will not favorably affect his condition inasmuch as nicotine is regularly absorbed from the oral mucous membrane.

Question: Is there a safe number of cigarettes to smoke? Suppose I bring my smoking to this level, may I then continue to smoke?

Answer: For all practical purposes there is a safe level of cigarette smoking, at least a statistically safe level—under five cigarettes a day. However, I have yet to find a confirmed cigarette smoker (a pack or more a day) who has been able to bring his smoking to this level and hold it. For this reason I suspect that those who smoke five cigarettes a day have never smoked more and probably should not be classified as "smokers."

Question: Is there a filter cigarette that is safe to smoke?

Answer: There is no evidence that any filter currently on the market provides significant protection against the hazards of smoking. If a filter removes substantial amounts of the tar fraction it *may* afford some protection against lung cancer and other diseases causally related to tars. However, the degree of protection has yet to be determined. It should be noted that there are many components of tobacco smoke (gas phase) unaffected by filters. To the extent that these are related to disease, filters will have no protective value.

Reinforcement

There is little question that certain individuals will require long-term reinforcement if they are to achieve lasting success as ex-smokers. Unfortunately we know far too little about the kinds of reinforcement that will best meet the needs of different types of smokers. One suspects that, with alteration of the social acceptability to smoking, the environmental influences (mass communications, peer group pressures, etc.) which now support the cigarette habit will begin to weaken and eventually reverse themselves and support non-smoking behavior. It is also likely that to the extent that smoking becomes unacceptable in any given setting there will be reinforcement of non-smoking behavior. If for example the patient appreciates that smoking is unacceptable in the medical setting whether this be private office, clinic or hospital, and if he knows that his physician disapproves of his smoking and wants to help him stop, this should reinforce his determination to stop. This, I suggest, is one powerful argument for the banning of smoking and the sale of cigarettes in all medical facilities.

With each office visit the doctor can provide reinforcement through the simple expedient of inquiring about the patient's progress. A genuine effort to stop smoking should always be warmly applauded. The mere anticipation that an inquiry will be made by the physician and his staff can be an important source of encouragement and support.

The attitude of the patient's family is of critical importance during and immediately following withdrawal. It has been our experience that a smoker's efforts may be unwittingly sabotaged by members of the family simply because they do not appreciate the significance of his battle and consequently look upon his withdrawal efforts with disinterest if not outright amusement. A brief word from the physician to one or more of the family may be all that is needed to provide an atmosphere within the home that is sympathetic and reinforcing.

Concluding Comments

There will be those who will continue to smoke despite our best efforts. It would be unrealistic to expect the busy office physician to work "miracles" with each of his smoking patients. Nevertheless there are many whom the doctor can help—with *minimal* intervention. Just getting a patient to stop ignoring his smoking problem may be all that is needed to start him on the road to success. This can often be accomplished with one or more simple yet firm admonitions to stop. Others will require additional aid. The physician should recognize that smokers differ in the reasons they smoke and consequently in the difficulties they will encounter in giving up the habit. It is for this reason that all smokers will not respond to a single therapeutic regime—just as all patients with chest pain will not respond to one form of therapy. When the physician recognizes this he will reassess his therapy rather than fault the smoker when he fails to respond.

Finally, I would simply reaffirm what every physician knows so well—that possibly the most important determinant of success in this as in so many therapies is the physician's own behavior and attitude toward his patient and his problem. If the doctor smokes, the patient will know this and may interpret such contradictory behavior as an automatic disclaimer of anything said on the subject. He may well reason: "If my doctor really believed what he was telling me he would not be smoking himself." Like it or not, here is an issue where patients expect their doctors to practice what they preach! I submit, therefore, that it is not unreasonable to expect every physician who smokes to make a sincere attempt to break the habit.

Equally important is the physician's attitude toward his patient. Here I would put forth a strong plea for a reduction in the desk-pounding "my-God-man-use-some-will-power" approach that seems to be the prevailing ingredient of some physicians' office programs. Firmness and direction are important. Equally important are genuine empathy and understanding. Optimism and constant encouragement should be the order of the day. If the physician becomes discouraged he must diligently disguise this. It is true that to date our "success" in helping smokers (at least in withdrawal clinics) appears to have been modest. But let us remember that there are many areas in medicine where we accept modest therapeutic successes without becoming prematurely discouraged. Need we look further than cancer of the lung!

Let us also remember that with smoking, as with all addictions, repeated episodes of "falling off the wagon" are to be expected before one is home free! This may temporarily discourage the smoker but should never mislead his doctor. On the contrary, an episode of backsliding can be used effectively as a means of reopening the issue and reinforcing the smoker's determination to conquer the habit once and for all. Above all let us not forget that smoking cessation has been scientifically documented as one of the most effective forms of chronic disease prevention at our disposal. For both doctor and patient, the pay-off of becoming an ex-smoker is clearly worth a maximum expenditure of effort. As one successful smoker aptly phrased it: "The juice is surely worth the squeeze!"

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Bad Health and Big Shots

The specialists inform me that almost everybody had syphilis in the sixteenth century, including Henry the Eighth, who also endured chronic, malignant wife-trouble. Charles V, Holy Roman Emperor of the German people, was strong, cautious, brave and wise, but he ate too much. If he had had a passion for Wheaties instead of roast pig the destinies of Europe might have been quite different. Samuel Pepys, whose lady-killing tendencies are now blamed on a scar in his perineum, was presumably saddled with gall stones (many eighteenth-century surgeons carried handfuls of gravel around in their pockets for display purposes if an operation failed to produce stones).

Edward Gibbon had an embarrassing what-is-it dangling around his knees, unwieldly as his Roman Empire. Martin Luther struggled along for sixty-two years with nerve trouble, ear trouble, blood trouble, and heart trouble. Henry Fielding thumbed his nose at gout and dropsy and wrote "Tom Jones" and "Amelia." Alexander Pope had spells when he couldn't stand unless laced in a frame. He averred that, at a distance, he looked like a small windmill. The mere mention of Thomas De Quincey's ailments makes hardened medicos grow pale, and yet this strange genius kept plugging for seventy-five years.*

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*Sprague, Marshall: The Business of Getting Well, 1943.

Physical Inactivity*

The Associated Cardiovascular Risk

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PHYSICAL INACTIVITY is in all likelihood a cardiovascular risk factor, to be listed along with the others which have been identified over the years. Thus Fox and Haskell,[1] who made a survey of the literature, stated the following tentative conclusion: "Those who are in physically active groups have fewer manifestations of coronary heart disease than those who are not" and "The amount of physical activity needed to decrease the risk of coronary heart disease may be acceptable to many." Kannel[2] reported from Framingham: "In this sedentary population, the most sedentary had a distinctly worse outlook." He also pointed to the problems in assessing physical activity and in obtaining, for such a study, really physically active adults. Morris[3] suggested that farmers in the central part of the United States are relatively protected against coronary heart disease and that this may be in part attributable to their physically active life. Epstein[4] has also summarized the literature and has written: "The evidence is in accordance with the hypothesis that physical activity and coronary heart disease are inversely related."

It has been said that coronary heart disease is a disease of a soft exercise-free mid-twentieth-century existence. Michaels[5] in discussing this concept has pointed out that this surely does not apply to the middle and upper classes, groups which in the past never have engaged in manual labor. He points out the abundance of domestic help in England and Wales in the nineteenth century (11.8% of the labor force in 1801, 14.1% in 1901) and the number of private carriages (437,602 in 1869). He also indicates that most of the sports were spectator sports (boxing, cock-fighting, badger-baiting). Viewing this problem somewhat differently, Cumming[6] has investigated the question of the fitness of youth and has concluded: "There is no proof that the youth of today are 'softer' than the youth of previous years. On evidence presented to date, highly civilized western men would seem to have aerobic capacities equal to those of men in primitive societies."

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*Much of this material has been published also in the section on Controversies in Cardiology of the American Journal of Cardiology.

Presented at the Minnesota Symposium on Prevention in Cardiology, May 2-3, 1968 in Rochester, Minnesota.

See editorial page 1209.

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Exercise Studies

Collateral Growth

Eckstein[7] has demonstrated, in dogs, that mild coronary arterial narrowing, as contrasted with moderate and severe narrowing, would not initiate collateral growth unless combined with exercise. On the other hand, Burt and Jackson,[8] also studying dogs but without actual coronary narrowing, concluded that exercise alone was insufficient to stimulate coronary collateral growth. Stevenson et al.[9] worked with rats and found that when the little animals were forced to run on a treadmill the coronary tree increased in size if the exercise was intermittent or only for a period of two weeks, but that when the same exercise was continued for longer periods of several weeks, no increase in coronary tree size was demonstrable.

Biochemical Changes

Nordoy, Newland, and Hamlin[10] studied the effects of treadmill exercise, both acute and long-term on rats fed a 40% butter diet. They reported that except for an increase in free fatty acids in acutely exercised rats, no changes were found in total cholesterol, phospholipids, triglycerides, and free fatty acids in the plasma. There was no difference in the incidence of adenosine diphosphate-induced thrombosis in the three groups with acute exercise, chronic exercise, and no exercise.

On the other hand, Nikkila and Konttinen,[11] studying 40 army recruits, found that after acute exercise the serum triglycerides were lower than in the non-exercised group. Dalderup, deVoogd, Meyknecht, and denHartog[12] reported that prisoners who exercised regularly achieved a slight reduction in serum cholesterol as compared with prisoners who did not participate in the program. Unfortunately, details as to the selection of the exercised and control groups are missing. Hoffman, Nelson, and Goss[13] found that the Canadian Air Force exercise program seemed to result in lower serum cholesterol and triglyceride levels in a population of Army officers. The differences reported were indeed minimal (cholesterol 213 in the exercised group, 223 in the controls, with triglycerides of 100 and 113 respectively). No true control group existed and the amount of weight change was not stated. Varnauskas, Bergman, Houk and Bjorntorp[14] studied nine patients with coronary disease in a four-to-six-week program of bicycle exercise and observed that exercise did not influence the serum level of cholesterol or triglycerides; indeed the cholesterol at the end was actually higher in five of the nine participants. McDonough and Hames[15] have suggested that seasonal variations in cholesterol levels in white and negro males were inversely related to exercise, but Thomas[16] did not find this to be the case in a population of Maryland prisoners.

Arteriographic Changes

Hellerstein et al.[17] reported that one patient developed, on repeat coronary arteriogram, clear evidence of an increase in coronary collateral circulation coincident with an exercise training program. A second patient in the program apparently showed marked clinical benefit and no coronary arteriographic evidence of the development of "an increased collateral circulation" although no control arteriogram was available.

Psychological Benefits

There is no controversy regarding this. All agree that regular physical activity leads to an increased sense of well being, more self confidence, and improved physiological measures of exercise tolerance. McPherson et al.[18] have recited some of the psychological benefits of an exercise program in 45 adult males, 18 of whom had experienced acute myocardial infarctions.

Pathological Evidence

Morris and Crawford[19] noted in 1958 that, on review of 3800 necropsies performed from 1954 to 1956 in Great Britain on males aged 45 to 70 dying non-coronary deaths, presumably ischemic myocardial fibrosis was commoner in those who had been engaged in light occupations than in those engaged in active and heavy occupations. It is interesting, however, to review the whole series of nearly 5000 autopsies available to them, which includes 1148 individuals dying from coronary heart disease (Table 1). When one does this, it is apparent that very modest differences are seen in the prevalence of coronary heart disease in the categories of latest employment described as light, active, and heavy.

TABLE 1
Frequency of Coronary Heart Disease (CHD) in Autopsy Reports on Men Aged 45-70
(1958 Brit. Med. J. *ii,* 1485)

Item	Activity, Last Job Light	Active	Heavy
Total autopsies	1922	1865	1092
Dead from CHD	482	436	230
Old infarcts, dead from other causes	51	28	10
Total CHD	533	464	240
CHD prevalence	27.7%	24.7%	22.0%

Epidemiologic Studies

There have been many epidemiological studies reported which appear to indicate that persons engaged in considerable occupational or recreational physical activity have a lessened prevalence and incidence of coronary heart disease; but not all such studies have reached this conclusion. Chapman et al.,[20] in a prospective study of 955 civil servants, found an excess of new coronary cases among those taking part in heavy physical exertion. However, their findings were based on only 37 new cases. Forssman and Lindegard[21] in 1958 studied a group of 66 males under 55 who had survived a myocardial infarction, compared them with 62 matched controls, and reported no differences in occupational physical activity. In 1960 Stamler[22] studied the mortality data in Chicago for the years 1951 and 1953 and wrote: "No specific occupation group differences in age-specific arteriosclerotic heart disease death rates were observed for middle-aged men." Pell and D'Alonzo[23] in 1961 studied 653 employees with myocardial infarction employed by the duPont Company, and found that the highest disease rate occurred among the lower middle salary group, whereas the lowest rates did not occur among those most physically active at work. In 1962, Acheson[24] was unable to observe any relation of physical activity before retirement with coronary disease as studied in a population of 221 men aged 65 to 85 years. Keys et al.,[25] studying clump samples in rural Finland, Holland, Yugoslavia, Italy, and Greece in 1966, found it very difficult to distinguish the roles of physical activity and socioeconomic status. Keys has shown that the more physically active Finns have more coronary deaths than we do (Table 2). Malhotra,[26] reporting from India in 1967 regarding railway employees, appeared to find a lower mortality among clerks than among more physically active sweepers and fitters.

TABLE 2
Deaths Per 100,000 Men 40-59
Age-Adjusted to U.S. White Age Distribution

Cause	Data	U.S. White	Finland
All causes	WHO 1962	1002	1165
Coronary (B26)	WHO 1962	371	405
All causes	Cohort*	922	1363
Coronary	Cohort*	308	421

*Five-year follow-up data from Keys, Taylor, Karvonen et al.

What about the studies which have reported a lessened morbidity or mortality from coronary disease in physically active populations? Breslow and Buell[27] in 1960 stated: "A gradient of decreasing mortality rates from coronary heart disease with increasing physical activity of work in middle-aged men . . . is confirmed under special conditions in California data for 1949 to 1954. The California gradient is clearly revealed only in contrasts between occupational groups of similar general mortality risk." They further state: "The recorded mortality data used here will not answer the question whether a limitation of physical activity is a real cause of coronary heart disease. Nor will it even provide a good estimate of the strength of the association between the two . . ." In a survey of 2240 letter carriers and postal clerks which he reported in 1963, Kahn[28] concluded: "The coronary heart disease mortality risk for those in sedentary work is between 1.4 and 1.9 times the risk of those who are more active on the job. . . ." The impact of this conclusion is blunted when we read in the next paragraph: "It is entirely possible that the differences observed are only coincidentally related to physical activity differences and that indoor versus outdoor activity, differential proportions of cigarette smokers, original basis of selection and so on are the really meaningful factors." This important matter of the original basis of selection is well illustrated by the analysis of the sedentary London bus drivers and the more athletic conductors described by Morris[19] as indicating the favorable coronary lot of the latter. As reported in 1960 (Table 3)[29] we find that the happy lot of the conductors actually may have been because they were less heavy and had less adiposity, lower serum cholesterol levels, and lower blood pressures.

TABLE 3

Mean Values, and % of Men Hypertensive, for London Busmen. D = Drivers, C = Conductors.
(1960 Proc. Roy. Soc. Med. 53, 18)[29]

	Ages 40-49		Ages 50-59	
Item	D	C	D	C
Relative body weight	101	90	101	94
Skinfold thickness	44	33	47	37
Serum cholesterol	249	228	254	238
% with B.P. 160/95 or more	10%	4%	29%	16%

In recent articles[30] Frank, Weinblatt, Shapiro and Sager have reported observations on some 110,000 participants of both sexes in the Health Insurance Plan of Greater New York. They reported: "A striking association between physical inactivity and early mortality from initial myocardial infarction in men less than 65 years of age has been shown." The data were derived from the first clinically manifest infarctions occurring in a population of some 55,000 male adults enrolled in the Health Insurance Plan of Greater New York during an observation period of 18 months (301 cases). Frank et al. also reported: "Physical activities off the job have been shown to play an important role in the relationship." I have not subjected their study to a penetrating analysis, but I am grateful to Dr. Ancel Keys for a valuable critique of this investigation. His analysis of the data leads him to have significant reservations regarding the conclusions cited above. His reservations pertain especially to problems in mail response vs. interview methods, the distribution of certain men whose physical activity was unclassified, and the existence of associations of levels of physical activity with race and religion.

In our Western Electric prospective study[31] we have 1719 men originally aged 40 to 55 who have now been followed for eight years, with the development of 24 coronary deaths, 53 infarcts with survival, and 80 cases of angina pectoris. To assess the validity of the Company codes for physical exertion in our shop population, Bliss and Graettinger[32] in 1964, using a random selection, studied 18 men in the shop working at a Code 2 level and 18 others working at a Code 4 level, using an impedance motor pneumotachograph. It was found that the men in Code 4 did indeed expend over 50% more calories than the men in Code 2. At the end of eight years there was no significant difference in the incidence of myocardial infarctions with survival in the shop and office groups as a whole, and only a slight and statistically insignificant difference of coronary deaths, with fewer being seen in the shop than expected (11 deaths as compared with 13 expected) (Table 4). After eight years, the more active Code 4 indeed

TABLE 4

		Non-Coronary	Angina	Infarct	Coronary Death	Total
Shop Code	1)	7	0	0	0	7
	2)	606	21	19	8	654
	3)	241	16	6	3	266
	4)	54	4	6	0	64
	5)	2	0	0	0	2
Office Code	1)	494	34	17	10	555
	2)	127	4	5	3	138
	3)	28	1	0	0	29
	4)	3	0	0	0	3
Total		1562	80	53	24	1718

showed fewer coronary deaths than the less active Code 2, but unfortunately also relatively more infarctions with survival.

Concluding Comments

There are basic difficulties with all such data, including our own:* the modest differences in occupational and non-occupational physical activity and the need to assess non-occupational physical activity, validation of questionnaires, the problem of occupational withdrawal, the distribution of risk factors in sedentary and physically active populations, and the differences in socioeconomic status. Suffice it to say that this list is incomplete. I should like to stress that we have no need to hedge regarding the epidemiological and other data relating hypertension and elevated serum cholesterol levels and also the heavy use of cigarettes to coronary disease and its complications. These associations have been decisively and repeatedly demonstrated.

I like physical activity. I believe it makes us and other patients feel better. I agree that it may contribute to the development of a collateral circulation in the myocardium and may be helpful in achieving satisfactory blood lipid levels through weight loss. However, the total evidence that regular vigorous physical activity per se lessens the likelihood of the development of coronary atherosclerosis and its complications is as yet not as impressive and as convincing as one would expect from the statements made by some of our scientific leaders and by statements in the mass media.

With our current knowledge of risk factors, any contribution made in minimizing the coronary problem through a routine of moderate regular physical activity is probably modest. It is possible that truly vigorous exercise, undertaken on a faithfully regular basis, may give more promising results; but we need more evidence of this.

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*I strongly suspect that in our study the men who do the heaviest work actually smoke more. We also have evidence in our population that men who moved out of jobs requiring the most vigorous effort later developed coronary disease.

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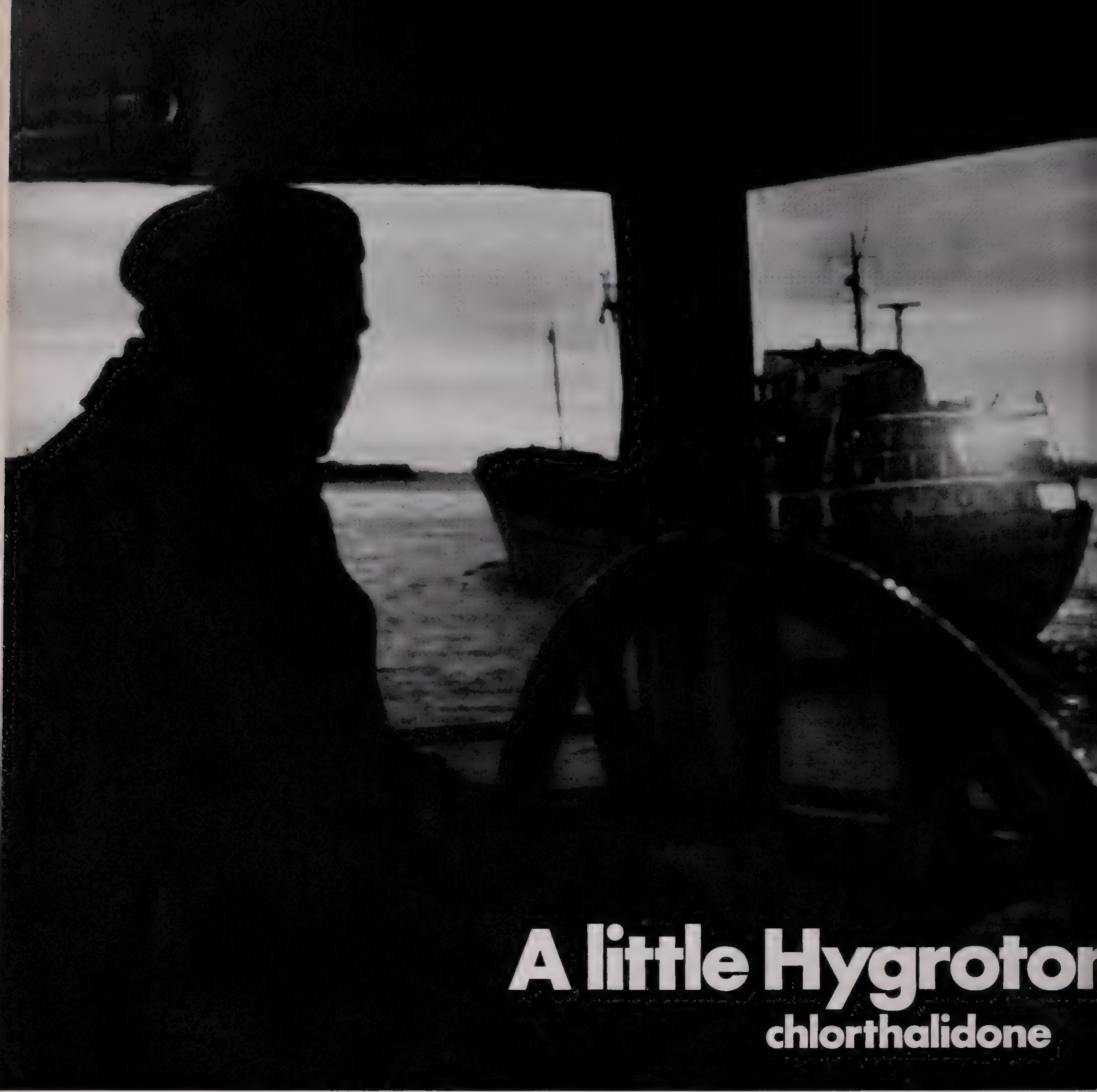
Thought

No one deserves the name of thinker until he dare think forbidden thoughts. We all do, but few of us dare admit it to ourselves. For the capacities of the human mind are limitless, and to try to limit them by a high board fence of veto, taboo, or dogma, is an attempt to rope off a stellar galaxy as a sheep pasture.

—Boston Globe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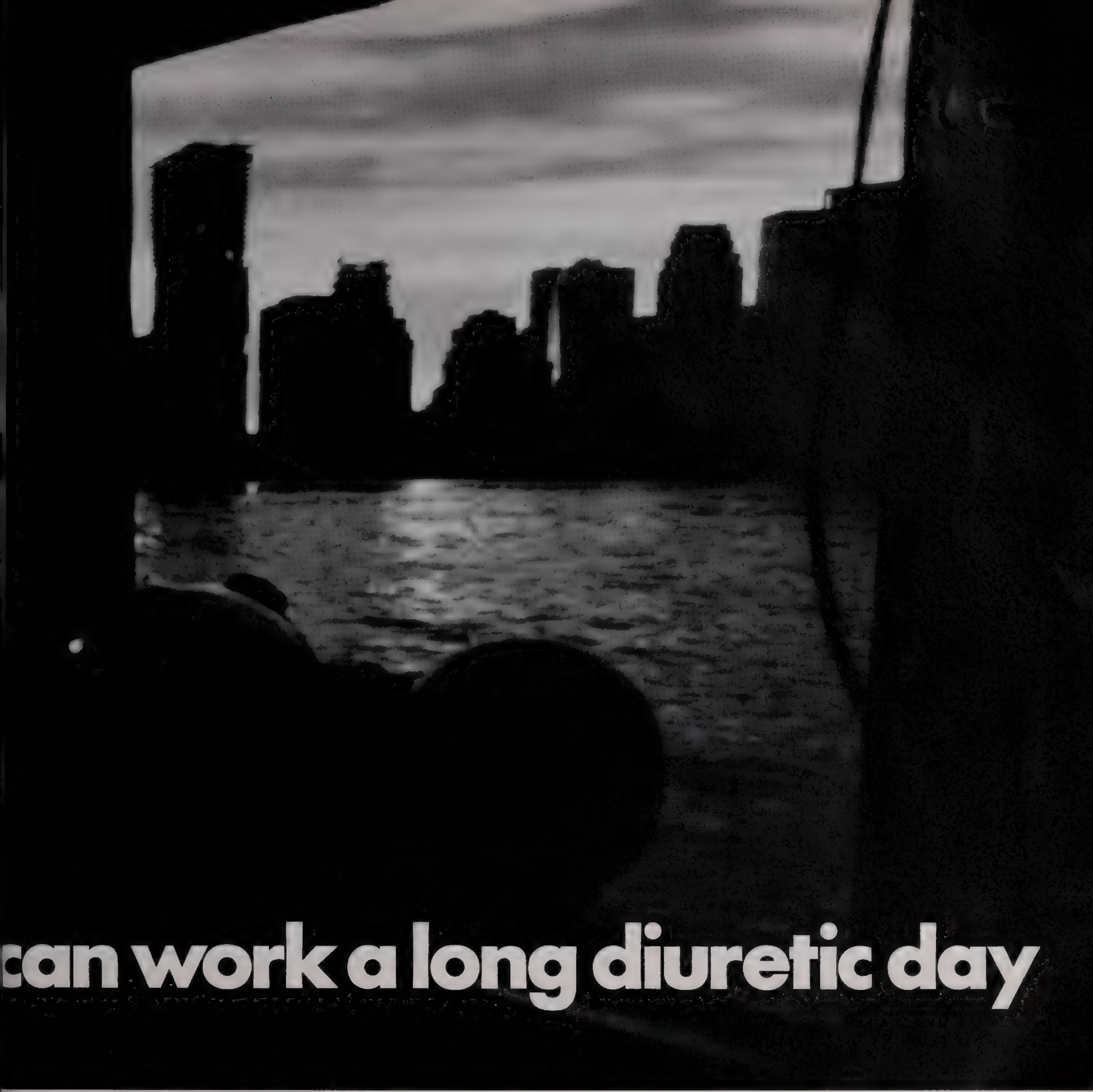

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The Effects of Physical Activity*

Patients and Normal Coronary Prone Subjects

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In the past six to seven years, my associates and I have been engaged in a prospective study to determine the feasibility and efficacy of activating habitually sedentary, lazy, hypokinetic, hypercholesterolemic, cigarette-smoking, hypertensive, overweight males, with or without manifest coronary artery disease, to participate in and adhere to a program of enhanced physical activity.[1] We hoped to determine whether such a program would be associated with some evidence of retardation of the effects of atherosclerosis, as manifested by a reduction in morbidity and mortality of coronary-stricken subjects and in the incidence of new thrombotic episodes in highly coronary-prone subjects. Therefore, the study population included both coronary-stricken and normal coronary-prone subjects. The inclusion of the latter was predicated upon the findings of prospective epidemiologic surveys.[2]

Design of the Study

The intervention program was multifaceted, the details of which have been presented elsewhere.[1,3] Emphasis was placed primarily on the enhancement of physical fitness. Physical reconditioning was a part of a comprehensive positivist program which included the improvement of nutrition, reduction of the intake of saturated fats, attainment of normal body weight, adequate rest and sleep, abstinence from the use of tobacco, and continuation of a gainful employment and of a normal social mode of life.

Methods

The evaluations were multidisciplinary and included the following data: detailed cardio-

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vascular history, physical examination, height, weight, somatotype, skin-fold measurements, estimation of obesity, serum cholesterol and triglycerides, timed vital capacity, psychological tests, resting and exercise electrocardiograms, and bicycle exercise ergometry. The majority of the participants were monitored for 48 consecutive hours by means of a portable electromagnetic tape recorder in order to characterize their responses to the stresses of everyday life activities.

Exercise Testing

Submaximal exercise testing on a mechanically braked bicycle ergometer (Monark, Sweden) consisted of intervals of six minutes of exercise alternating with four minutes of rest.[1,3,4] Work loads were progessively increased by increments of 150 KPM/min for each interval until a heart rate of 150 per minute was reached in the last two minutes of exercise. The electrocardiogram and arterial blood pressure were recorded at minute intervals throughout the pre-exercise, exercise, and recovery periods.

Physical Fitness

Physical fitness was characterized by the physiological variables, heart rate, blood pressure and their derivatives: heart rate × systolic blood pressure, Work Load 150, and predicted maximal oxygen uptake. Predicted maximal oxygen uptake per kilogram body weight (ml O_2/kg B. W./min) was calculated according to the method of Åstrand.[5] Work Load 150 per kilogram body weight (WL 150 KPM/kg B. W./min) was calculated according to methods previously described.[4] A minimal heart rate of 135 was used to extrapolate to Work Load 150. An indirect measure of myocardial oxygen consumption was obtained from the product of heart rate and systolic blood pressure computed for the last minute of exercise at each work level.[4]

Electrocardiogram Evaluation

Electrocardiograms were analyzed according to the methods of Lester et al.[6] in terms of the ST-J displacement and the slope of the first 0.08 seconds of the ST segment.[7] We considered quantitation of the electrocardiogram response to be important, since Robb and Marks[8] have reported that the prospective mortality rate was directly related to the magnitude of the displacement of the ST segment with a zero or negative slope. The electrocardiograms were evaluated in the same manner and comparisons between tests were made for the same load at identical external work loads.

The Subjects

The subjects of the intervention study were white, middle-aged, middle and upper class men who were referred to the program by their physicians. They continued to look to their private physicians for their overall medical care. At the onset of the feasibility study, we made no attempt to gather a true random sample or a "control" group. Our comparison group consisted of 194 coronary-stricken, age, sex and color-matched subjects concurrently evaluated in a work classification clinic. They were followed over the same period of time as the intervention subjects.

Of the 656 subjects in the intervention program, 402 were categorized as normal coronary-prone subjects, and 254 as having coronary heart disease (angina pectoris documented myocardial infarction or both). None had congestive heart failure. The coronary-stricken subjects have been followed for a total of 697 subject years, with an average of 2.7 years. At the time of the intake into the study (documented myocardial infarction, or both) the average age of the normal coronary-prone was 45 years and of the coronary-stricken 48.8 years; since the age of 25 years, the body weight had increased on an average of 19 pounds; 28 per cent of the subjects were more than 15 per cent overweight. The overall physical fitness was low and averaged 25 ml. oxygen/kg.B.W. Thirty-two per cent of the subjects were professionals (physicians, dentists, engineers, pharmacists, lawyers), 22 per cent managerials, 20 per cent businessmen and executives, 17 per cent salesmen, and the remainder semi-skilled workers. Only one per cent was unskilled. They worked more than 50 hours a week. Forty-seven per cent smoked cigarettes. Seventy-two per cent possessed the behavioral characteristics of Type A personality, classified according to the method of

Rosenman and Friedman.[9] In general, their scores on the depression (D), hypochondriasis (HS) and hysteria (HY) scales of the Minnesota Multiphasic Personality Inventory were elevated.[1]

Methods of Conditioning.

Following the evaluation of each subject, a program was formulated to enhance his overall fitness. The subject met with a study physician and a physical educator who reviewed with him the results of all tests performed, answered any questions, and prescribed for him a specific exercise program. The exercise prescription, consisting of walking, running and calisthenics, was compounded to stress each subject at approximately 60 to 70 per cent of his aerobic capacity.[4] The caloric expenditure of full participation totalled approximately 400 calories per hour. Calisthenics required 200 calories over a 30-minute period, run-walk sequences, 120 calories over a 15-minute period, and recreation, 80 calories over a 15-minute period.[1] The normal coronary-prone and coronary-stricken subjects participated in the same calisthenic groups, each following his own prescription. There are 21 lay exercise leaders, of whom five are coronary-stricken subjects.

In addition, the subjects were advised to be active physically, to climb stairs, to avoid the use of the elevators, to walk instead of riding a vehicle, to park further away from the parking lots, etc.

Each subject was encouraged to attend exercise classes at the Jewish Community Center of Cleveland at least three times a week. The subject kept a record of his attendance and made a note of comments or reactions to the exercise program. A staff physical educator examined the records kept by the subject at monthly intervals and determined whether he was ready to progress to a more strenuous level of work. Coronary-stricken subjects were carefully supervised during exercise by specially trained physical educators. In many subjects, the electrocardiogram was telemetered during the exercise sessions and usually showed significant displacement of the STT segment or arrhythmias (Figure 1). Adherence to the exercise plan was graded independently by the study physical educator who reviewed the attendance records but did not have knowledge of the heart rate, blood pressure or electro-

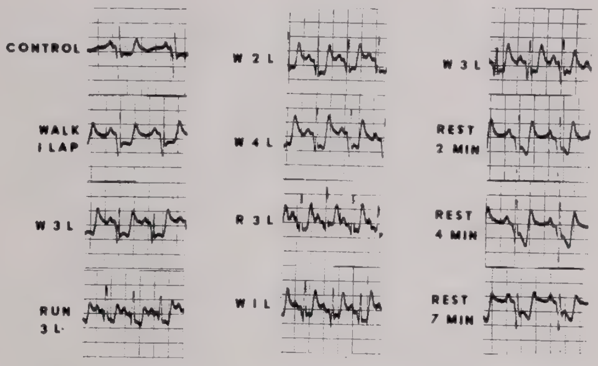

Fig. 1—Radio-transmitted electrocardiograms recorded during walking (W) and running (R) of a cardiac subject. Note that ST displacement decreases when the subject runs and recurs at rest. (L indicates 1/18 of a mile).

(Previously appeared in the following article:
Hellerstein, H. K. Exercise Therapy in Coronary Disease. New York Heart Association, Inc., Conference on Coronary Heart Disease: Preventive and Therapeutics Aspects. Reprinted from Bulletin of the New York Academy of Medicine Second Series 44:8, pp. 1028-1047, August, 1968).

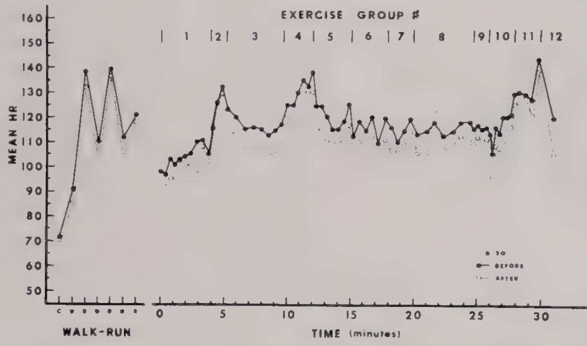

Fig. 2—Average heart rates of walk-run sequences (W = walk, R = run, C = control) and of consecutively performed calisthenics done routinely in the Case Western Reserve University Physical Conditioning Program.

The electrocardiograms of twenty subjects (average age 48 years) were telemetered before (solid lines) and several months after (dotted lines) participation in the program. Note that the average heart rate was almost 120 beats per minute, representing 70 per cent of their predicted maximal heart rate. Exercise numbers signify performance of the following exercises: (1) shoulder exercises, standing, warm-up; (2) hops, walk steps; (3) arm sweeps, standing; (4) hops, sailor's hornpipe; (5) body bends; (6) leg exercises, supine; (7) leg-arm-hip exercise, sitting on floor; (8) leg exercises, lying on side; (9) leg exercises, bicycle movements, supine; (10) sit-ups; (11) push-ups; and (12) shoulder exercises, standing, cool off.

cardiographic responses to bicycle ergometry. Grade 1 represented minimal or no participation, grade 2, 0.5 to 1.5; grade 3, 1.5 to 2.2; grade 4, 2.3 to 2.6; and grade 5, 2.7 or more (up to 5) hours per week of running and calisthenics.

In general, during calisthenics, the average heart rate was 120 beats per minute, which represent 70 per cent of the predicted maximal heart rate of subjects 45 to 50 years of age (Figure 2); during the run-walk sequences, heart rates of 145 to 150 were attained, approximating 85 per cent of maximal heart rate.

Results

The results of the active intervention program on a subgroup of 100 coronary-stricken and of 58 normal coronary-prone were analyzed in greater detail.[7] The average period of followup was 33 months. The average loss of body weight was approximately five pounds in both the coronary-stricken and the normal coronary-prone.

Serum Cholesterol

Serum cholesterol dropped significantly from an average of 263 to 242 mgm/dl, $p < .05$. Many subjects improved their physical fitness but did not reduce serum cholesterol unless they adhered to a fat-restricted diet. As noted previously, the serum cholesterol dropped significantly in the adherent group, $p < .001$, but not in the partial and non-adherents, $p < .2$.[1]

Physiologic Data

The physical fitness at the time of the initial evaluation was low compared to other populations[5] but similar in both the normal coronary-prone and coronary-stricken, i.e., 24.6 and 23.8 ml O_2/kg B.W./min., respectively. Physical fitness improved in a similar number of the normal coronary-prone (71 per cent) and of the coronary-stricken (64 per cent). The average oxygen uptake increased comparably (20

TABLE

Effect of Physical Conditioning on the Physiological Parameters (Heart Rate, Blood Pressure, HR X SBP, Work Load 150, Predicted Maximal Oxygen Uptake) of 100 Men with ASHD and 58 Normal Men

	ASHDs						NORMALS					
Change in Fitness		INITIAL		FINAL				INITIAL		FINAL		
	N*	Mean	S.E.†	Mean	S.E.	p‡	N	Mean	S.E.	Mean	S.E.	p
HEART RATE												
Improved	64	129.2	2.1	112.0	1.9	<0.001	41	140.0	2.8	121.4	2.8	<0.001
No Change	17	122.3	5.7	119.2	4.6	NS#	8	127.2	10.3	122.2	8.2	NS
Worsened	19	124.3	4.4	127.7	3.9	NS	9	136.5	6.7	140.7	5.9	NS
BLOOD PRESSURE (mm Hg)												
Improved	64	191.3	3.1	171.6	2.9	<0.001	41	191.7	3.8	174.4	3.4	<0.001
No Change	17	181.1	8.1	184.0	9.3	NS	8	183.2	8.2	194.2	11.1	NS
Worsened	19	170.5	5.3	189.9	6.5	<0.001	9	182.1	9.2	201.1	9.1	<0.005
HR X SBP§												
Improved	64	248.3	6.4	192.7	5.3	<0.001	41	270.3	8.2	211.1	7.4	<0.001
No Change	17	225.4	18.2	223.9	18.1	NS	8	233.2	20.1	237.8	20.9	NS
Worsened	19	212.9	11.0	243.8	12.0	<0.001	9	246.3	17.3	283.1	17.9	<0.001
WORK LOAD 150 (KPM/kg B.W./min.[1]												
Improved	40	8.2	0.2	10.3	0.3	<0.001	35	7.9	0.3	10.4	0.3	<0.001
No Change	9	7.6	0.4	8.4	0.3	NS	4	9.3	1.2	10.0	0.8	NS
Worsened	9	7.8	0.6	8.9	0.6	NS	5	10.3	0.6	9.8	0.6	< 0.05
PREDICTED MAXIMAL OXYGEN UPTAKE (ml O_2/kg B.W./min.)												
Improved	57	23.4	0.5	28.1	0.6	<0.001	37	23.7	0.8	28.6	1.0	<0.001
No Change	14	24.6	1.2	24.8	1.0	NS	7	27.3	1.4	28.4	1.9	NS
Worsened	12	25.0	1.5	25.6	1.4	NS	5	27.0	1.5	26.8	1.7	NS

*Number of subjects attaining necessary heart rate for extrapolation, i.e., 135 for calculation of Work Load 150, 120 for calculation of Predicted Maximal Oxygen Uptake.

†Standard error of the mean.

‡Determined by the t test for paired samples.

#Not significant.

§ $\times 10^2$.

per cent—to 28.6 and 28.1 ml O_2/kg B.W./min., respectively) in both groups (Table).

Individual subjects showed noteworthy and exceptional improvements in performance. One 45-year-old executive with a posterolateral myocardial infarct regularly runs five to 10 miles several times a week, and is currently training for a well known marathon. He was telemetered during a five-mile run in 39 minutes, during which time he developed a heart rate up to 170 per minute without arrhythmias or ischemic manifestations.

The systolic blood pressure response to exercise was lower in the normal coronary-prone when compared to the coronary-stricken at the same work load.

In the improved fitness subjects, in addition to improvements of predicted maximal oxygen uptake and W.L. 150, decrements occurred for the same work level for the exercise heart rate, blood pressure, and heart rate times systolic blood pressure product, at highly significant levels, $p < .001$ (Table). The resting blood pressure decreased from 129.9/86.8 to 121.7/84.3 mm Hg., $p < .01$. In general, the improvement of exercise heart rate and blood pressure were concordant; however, approximately 20 per cent of the subjects whose heart rate response during exercise improved, failed to show an improvement of blood pressure.

Changes in Exercise Electrocardiogram Categories and Physical Fitness

Both the normal coronary-prone and coronary-stricken subjects showed an increased amplitude of the T waves as the heart rate decreased with training. Improvement in the exercise electrocardiogram was related to improvement in physical fitness. In the coronary-stricken the initial exercise electrocardiograms were abnormal or borderline in 49 per cent, normal in 48 per cent, and showed U-shaped ST segments in 3 per cent. The number of normal coronary-prone with initially abnormal exercise electrocardiograms (4 of 59) was too small to analyze for significant relationships. Eighty-four per cent of the coronary-stricken subjects with initial borderline or abnormal electrocardiogram who improved their exercise electrocardiogram also improved their physical fitness. *Seventy-nine per cent of coronary-stricken subjects who improved their physical fitness also showed improvement in their exercise electrocardiogram,* whereas only 31 per cent of coronary-stricken subjects who did not improve their physical fitness or who worsened it showed improvement in their exercise electrocardiogram ($p < .003$).[7] In the entire coronary-stricken group, irrespective of initial electrocardiogram category, electrocardiographic improvement occurred in 41 per cent of subjects in the improved fitness group, and in 14 per cent of those in the not improved or worsened physical fitness group, $p < .003$. Electrocardiographic deterioration occurred in 18 per cent of coronary-stricken subjects in the improved fitness group and in 44 per cent of those in the not improved or worsened physical fitness group, $p < .05$.

In coronary-stricken subjects with improvement of exercise electrocardiogram, the mean ST J displacement decreased from 1.74 ± 0.34 mm to 0.78 ± 0.16 mm, $p < .001$. The mean slope increased from 0.16 to ± 0.18 mv/sec to 0.91 ± 0.13 mv/sec, $p < .001$.

Similar percentages of coronary-stricken subjects improved their physical fitness whether the initial exercise electrocardiogram was normal, borderline, or abnormal. Physical fitness improved in 28 of 48 subjects (58 per cent) with initial normal exercise electrocardiogram, and in 33 of 49 subjects (67 per cent) with initial abnormal or borderline exercise electrocardiogram.

The normal coronary-prone failed to show significant changes in ST J displacement or ST segment slope to produce a change in electrocardiogram category.

Adherence to the Exercise Program

In general, the adherence to the training program was better than that reported by others. Sixty-eight per cent of the subjects adhered to a training program of two or more hours per week, for an average followup period of 33 months. Subjects with adherence Grades of 5, 4, and 3 showed similar degrees of improvement in physical fitness and similar low rates of deterioration.

Improvement in physical fitness was related to adherence to the exercise program. In the coronary-stricken, improvement in physical fitness occurred in 86 per cent (30 of 35), 69 per cent (9/13), 71 per cent (12/17), 27 per cent (3/11), and 35 per cent (6/17) of subjects with Grades 5, 4, 3, 2, and 1 adherence respectively. The difference in improvement between adherence grades 1 and 2 vs. the grades 3, 4, and 5 groups was significant, $p < .003$. Improvement in the exercise electrocardiogram was similarly related to adherence to the exercise program. Of the subjects with initial abnormal or borderline exercise electrocardiogram, improvement in the exercise electrocardiogram occurred in 64 per cent (9/14), 67 per cent (6/9), 75 per cent (9/12), 50 per cent (3/6), and 25 per cent (1/4) of subjects with Grades 5, 4, 3, 2, and 1 adherence respectively. Deterioration of physical fitness or of the exercise electrocardiogram of the coronary-stricken occurred more frequently in the low adherence groups.

The normals (normal coronary-prone) also demonstrated a similar tendency for improvement in physical fitness to be related to adherence to the exercise program, and for deterioration of the exercise electrocardiogram to be related to lack of adherence. However, these changes were not statistically significant.

Several subjects have failed to show improvement in their physical fitness, despite strict adherence to the training program. Coronary arteriograms have shown severe narrowing (75 to 90 percent) of two major vessels and 50 or more per cent narrowing of the third vessel. Apparently the limiting factor was a lack of significant source for collateral formation.

Cardiac catheterization studies on seven subjects before and after training have shown reduced heart rate, increased stroke volume and unchanged cardiac output after training.

Deaths

In the present study, the overall mortality rate was 2.1 per 100 coronary-stricken subject years. Of the 194 coronary-stricken subjects in the comparison group, the mortality rate was 3.5 per 100 subject years. In other studies (Feil), the death rate has been reported to be five or higher. [10]In the normal coronary-prone, the death rate was 5 per 1000 subject years, which is less than the expected mortality rate expected for men of this age group in the United States. However, the number of the normal coronary-prone group is small. No statement of significance is warranted because a true "control" population was in this feasibility study.

Discussion

This study demonstrates that an active intervention program of physical conditioning, including prescribed, supervised exercise, weight reduction and diet therapy is feasible and acceptable, and appears to be of benefit in the therapy of subjects with coronary heart disease (without congestive heart failure).

The major determinants of successful physical reconditioning include a comprehensive approach, adequate and enthusiastic staffing, motivation of the study subjects and substantial adherence, systematic and repeated evaluation and counselling, and viable myocardium and adequate arterial sources to enhance the coronary circulation.

The beneficial mechanisms of physical conditioning have not been clearly elucidated. The similarity of the improvement in circulatory functions in the coronary-stricken and normal coronary-prone implies similar adaptation of the heart, of the periphery (skeletal musculature), and of the nervous system (baroreceptors, reflexes, etc.). Several studies have demonstrated improvement in the coronary arterial circulation in the dog and rat.[11,12] Although one of our subjects showed increased coronary collaterals after conditioning,[1] we have been impressed by the fact that marked improvement of aerobic capacity has occurred in some of our subjects whose post-training coronary arteriograms have shown no evidence of grossly visible collateralization. There has been no evidence of reversal or coronary atherosclerosis in our subjects. Whether the reduction of serum cholesterol and of triglycerides (in other studies) has retarded the atherosclerotic process is unproved. The psychologic changes are striking, with lessening of depression,[1] and improvement of self-image, insight and marital relations.[13] Many of the coronary-stricken subjects have indicated that they conceive of themselves as being less disabled after physical conditioning. Claims have been made that they "think" and even hear better!

The reduction of the heart rate and blood pressure and of myocardial oxygen needs at rest and during effort, and the improvement of stroke volume, dp/dt, and mood suggest a change in catecholamine metabolism turnover or storage, possibly in both the sympathetic nervous system (in the heart) and the central nervous system. Other studies have shown that coronary-stricken subjects release greater amounts of catecholamines after effort or emotional stresses. The higher-exercise heart rate and blood pressure of our subjects confirm this finding. In addition, Schildkraut and Kety have indicated that the biogenic amines of the brain are reduced in depressed states.[14] The present study suggests the possibility that there is an interrelationship between the psychologic and circulatory changes after physical conditioning. However, the nature of this relationship—coincidental or correlative—has not been clarified and remains conjectural at this time.

Unsolved Problems

Before large scale programs of physical conditioning are undertaken, more information is needed in regard to: selection of subjects, criteria for exclusion, scientific bases for exercise prescription and proscription, time of onset of program, duration and frequency of exercise for optimal effects, endpoints to stop exercise, monitoring devices, enhancement of motivation and adherence, and evaluation techniques. My associates and I have been impressed by the hazards encountered by subjects who ill-advisedly have joined in an unsupervised jogging program, without preliminary medical evaluation. Mass prescription of exercise for middle-aged subjects, many of whom have silent coronary artery disease, is justified only if techniques and facilities are made available for comprehensive cardiovascular evaluation, including multilevel exercise testing and electrocardiographic recording.

Summary

The present study of 402 normal coronary-prone subjects and of 254 coronary-stricken subjects demonstrates that a supervised program of physical conditioning improved both the physical fitness and the exercise electrocardiograms of coronary-stricken subjects and tended to prevent the deterioration of the exercise electrocardiogram in normals. Improvement in both physical fitness and the exercise electrocardiogram was a direct function of adherence to the program. Although the present report deals with an uncontrolled feasibility study, it would appear that an active conditioning program can be used safely in the treatment of selected coronary-stricken subjects without congestive failure, and in the reconditioning of normal coronary-prone men.

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A good dinner sharpens wit, while it softens the heart.—Doran.

Reducing Cardiovascular Risk*

The Basis and Feasibility

JEREMIAH STAMLER, M.D.†
Chicago, Illinois

I THINK WE CAN best distill what we have learned here by posing a series of questions and answers.

Is a Preventive Effort Needed?

The answer is "yes." The nature of the adult cardiovascular problem today in our country and in other economically well-developed countries is such that without a preventive effort we cannot achieve a decline in these diseases. This is based on the data on sudden death, mortality with the acute coronary event, prognosis after the acute event, and estimates of the potential of coronary care units.

How Adequate Is Our Preventive Effort

Based on Dr. Wilber's data it is obvious that not more than 10 per cent of the total number of hypertensives in our population are under adequate care. The figure is similar for diabetes in our communities and worse for hyperlipidemia. If we look at the data of the Coronary Drug Project, we see that approximately 50 per cent of this large group of coronary cases are still smoking cigarettes and about as many are overweight. Therefore I do not think that at the present time the long-term preventive effort, either primary or secondary, is adequate. There is a need for a preventive effort in terms not only of the nature of the problem but also of the adequacies of the current effort.

The overwhelming bulk of our medical practitioners today, generalists and internists, the army who must contend with this problem, are preoccupied with the care of people who are ill; and when we talk about a primary preventive effort, we are talking about an additional load of long-term medical care. All of the people in the practice of medicine admit they are involved very little in this kind of effort. No one believes that the current effort is adequate except for those who find the idea of a preventive effort absurd.

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*Presented at the Minnesota Symposium on Prevention in Cardiology, May 2-3, 1968 in Rochester, Minnesota.

†Executive Director, Chicago Health Research Foundation.

Is a Preventive Effort Justified?

It is true that field trials are needed to prove unequivocally that interference with cigarette-smoking habits, elevated blood pressure, and elevated serum lipid level will, indeed, alter the natural history of this disease. Despite the overwhelming and consistent mass of evidence on risk factors, as long as these final proofs from definitive mass field trials are not available, one cannot make categorical statements, based on present knowledge, that preventive programs are justified. One has to make a qualified statement, and I think that the position taken by the American Heart Association, by the Council on Food and Nutrition of the American Medical Association, by the Second National Conference on Cardiovascular Diseases and by the President's Commission on Heart Disease, Cancer and Stroke is very sound: namely, that the great bulk of evidence indicates the possibility of prevention. Hence it seems wise to proceed, in view of the scope of the problem and the need for primary prevention, and the fact that much of the preventive effort is nutritional and hygienic and therefore relatively safe, with drugs secondary and adjuvant. There is no indication that the trend of coronary disease will decline without such endeavors. My answer to the question is: Yes, prevention is justified, based on present knowledge and for the reasons that there is great evidence for the possibility of prevention and that the measures to attempt realization of that possibility are highly safe. I would add, however, that we need to proceed to get the field trials finished so that we can answer the questions more definitively.

Physicians, internists, cardiologists and local heart associations have a deep stake in the advances achieved by field studies such as the Coronary Drug Project. As a result of these studies definite guidance in treatment is obtainable, and it is therefore in their own interest to cooperate as fully as they can. Take also the example of the Cooperative Veterans Administration Study on therapy of moderate hypertension. Prior to its positive result, some physicians maintained that treating moderate hypertension was ineffectual and might even do harm: a valid position until the Veterans Administration Study. The small clinical studies on 20 to 30 patients a year, showing that drugs lower blood pressure or lipids, tell us nothing about the long-term effect of toxicity, survival, or reduced attacks. I think the entire community should be delighted in the laborious studies supported by the National Heart Institute and the Veterans Administration, and by the patience and cooperation of the medical profession and participants.

What Should Be the Main Thrust and Strategy of the Preventive Effort?

The thrust of the main effort for prevention must be treatment *before* illness. A second but very important thrust is the effective, long-term care of those who have been acutely ill but have recovered. I am grateful that my relatively short life in medicine has given me the opportunity to know Paul White and appreciate his lesson on the importance of long-term follow-up and care.

We have to formulate a strategy and fight for it. We are dealing with a disease that has a mortality rate of 600,000 per year, 165,000 under age 65. It is a war which will never be won without a strategy which is explicit, formulated and fought for in order, among other things, to get the resources which are needed. It is very easy for the public to be misled as to the central strategy in dealing with the heart problem. And if the public is misled, then it will also become confused and money will be wasted on causes which are not really justified or are secondary to the preventive effort needed. These issues have to be debated in public, decisions reached, and policy-making bodies influenced.

The second element of strategy is the maintenance and fostering of a social approach to the problem. The history of medicine teaches us that epidemic disease is never solved exclusively by an approach between the individual physician and his patient, as important a contribution as that is. TB was not solved that way, nor pellagra nor scurvy nor rickets, typhoid, polio, etc. The mechanisms of society as a whole have to be intermeshed with the approach of the individual and his physician. In our country, traditionally, the social approaches have always been two-pronged when they have been successful. On the one hand they have been governmental—federal, state and local—and on the other hand, voluntary. We now find this epitomized in the approach of the American Heart Association and the Regional Medical Program which is federally financed but emphasizes local initiative, coordination and cooperative planning.

The third and final element of strategy takes into account the special aspects of our adult population. Millions of Americans do not present themselves to physicians from one year's end to the next. There are millions of people who are walking around nurturing their coronary risk factors, prior to developing an acute and all too often fatal event. I know of no way to cope with this problem except through the systematic development of mass detection efforts of a public health nature, through non-M.D. personnel: primarily, technicians, nurses, especially trained nurses' aides and technician-aides, and others who will go among the population as we have been doing in Chicago, find what is wrong with them and bring them into the physicians for long-term care.

What Are the Elements of a Preventive Program?

Diet is of great importance, since it influences at least four of the risk factors that concern us. It influences all aspects of hyperlipidemia; it is related to obesity, and also to the risk of hyperglycemia and hypertension. There are many middle-aged hypertensives and diabetics who will be corrected by an effective diet alone.

The American Heart Association Diet as recommended for the last several years is a good foundation, moderate in calories to correct overweight and keep it corrected, moderate in total fat (30-35 per cent of calories), low in saturated fat and low in cholesterol and moderate in salt, at the 5 gm. level where there is a reason to control salt intake. The American Heart Association diet is a good diet for managing almost all types of hyperlipidemia; it is fine for obese adults, hypertensives, diabetics and their families.

In addition to diet the more effective control of cigarette smoking is essential. Cigarette smoking rates are highest today in men and women under 40. This means that a good number of middle-aged men have discontinued smoking, so that however vast the problem, there is a possibility of making progress against it with skill, persistence, sound public policy and a long-term approach.

Further, I think those of us who have been preoccupied with the lipid question have tended to forget the importance of hypertension in all areas and conditions of life. Hypertension can be controlled in a great majority of patients with modern drugs, and this control can be sustained. It does influence prognosis. We must emphasize hypertension much more as a risk factor and therefore its earliest possible detection and its effective long-term management. It is a sad situation when large numbers of people do not remain under long-term management because they are not given to understand the need to do so. The economic problem can be solved by dollars; the confusion problem is more difficult. It depends first and foremost on the physician. About exercise, I think there should be a rational and cautious approach until more knowledge is acquired.

What Is the Role of Pharmacology?

If industrial civilization with its rich diet, its sedentary living, its smoking, and its tensions has given us epidemic coronary disease, then I cannot believe that drugs are main answers. That is why I emphasize what might be called the nutritional, hygienic and social approach, and relegate pills to a contributory role based on the specific needs of individual patients.

Is Such a Preventive Effort Possible?

Given adoption of a correct strategy, a key step is detection effort to find the people at highest risk. We have the scientific and technological means to do this. The second element is the long-term sound effort to change habits and thus correct risk factors.

From our experience with the Diet-Heart Study and from experiences in Scandinavia, Britain, Chicago and New York, we know that large numbers of adults are prepared to participate in such efforts and that in a sizable proportion of them sustained participation will be reflected in such simple measurements as weight, serum cholesterol, blood pressure and even smoking patterns. Thus the challenge faces us, and the public is willing.

What Are Reasonable Perspectives for the Coming Years?

We are tackling a problem as tough in its social roots and its vastness as the tuberculosis problem was. To build on a firm foundation, and to build steadily, we must step-by-step diminish the smoking prevalance rate in middle-aged men, 10 per cent per year, increase the number of well-managed hypertensives by 10 per cent per year, etc. Despite sloth and gluttony, I am convinced that we will have no trouble in winning, granted some remnants of sanity still prevail in the world.

When the Brain Sleeps

The water hemlock, also known by its Latin name of *Cicuta virosa*, has its place in legends as the poison that cut short the life of Socrates, the famed ancient philosopher, who was made to take his own life while in prison.

The water hemlock occurs in the Soviet Union. It is widespread in the Urals, the Far East, the Karelo-Finnish S.S.R. and, to a lesser degree, in the Moscow region. Its root looks much like the root of parsley, and is often mistaken for it, and eaten. The result of such a mistake is fatal.

Doctor Ror works at a polyclinic in Verkhnaya Tavda, a Urals town. The water hemlock is often met in its neighborhood, and victims of the murderous plant are quite frequent there.

In such cases Doctor Ror, like any other doctor would in her place, did everything in her power to save the life of her patient. She injected camphor and caffeine to stimulate the heart and respiration, she applied artificial respiration, administered tannin, and did everything else that could bring some degree of relief. But medicine is helpless against the Cicuta poison. And whenever a patient came to the casualty ward whose body was in convulsions, who foamed at the mouth, whose face was blue, who was unconscious and whose pulse was so weak that it could scarcely be felt, and whose breath was nothing more than a death-rattle, it was clear to the physician that his case was hopeless.

A patient was brought to Doctor Ror on July 7, 1947. He had eaten water hemlock. His respiration was weak, there was foam at his mouth and he had cramps at five-minute intervals. In half an hour, an hour at most, he would be a corpse.

But in six hours the patient was out of danger, and in another three days he was discharged. In six weeks, when Doctor Ror saw her patient again, she could scarcely believe that this strong-looking chap, who was the picture of health, had only recently been at death's door.

Doctor Ror had read of Professor Galkin's* studies a few days before the hemlock victim was brought to her. She did not hesitate, therefore, to apply anesthesia. There was nothing to lose anyway: Life was fast ebbing in her patient.

The ether anesthesia lasted six hours with brief intervals. When Doctor Ror decided that the poison had been expelled from the organisms, she terminated it.

In July, August, and September 1947 three more Cicuta victims were saved in a similar way.†

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* Professor Galkin, a Leningrad patho-physiologist, discovered an amazing phenomenon: Many properties of the organism undergo great changes under the effects of narcotic sleep. Anesthetized cells can live under conditions that would be fatal to them under ordinary circumstances.

† L. Fridland, M.D.: The Achievement of Soviet Medicine, Edited by W. Horsley Gantt, M.D., 1961.

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Description: FLUOGEN (Influenza Virus Vaccine, Bivalent, Ether Extracted Antigen) (Types A_2 and B) is composed of the antigen of the strains of influenza viruses recommended by the Division of Biologics Standards, National Institutes of Health, Public Health Service. It is formulated to contain 400 CCA (chick cell agglutination) units of extracted immunizing antigen of type A_2/Aichi/2/68 strain (Hong Kong variant) and 300 CCA units of extracted immunizing antigen of B/Massachusetts/3/66 strain for a total of not less than 700 CCA units per each 0.5 cc. dose. **Method of Preparation:** The influenza viruses are propagated on developing chick embryos. The extra-embryonic fluid containing the virus suspension is harvested, clarified by filtration and concentrated and refined by ultracentrifugation. Polysorbate-80, U.S.P. (175 mcg. per 0.5 cc.) is added to the refined concentrate. The refined concentrate is extracted with ethyl ether, stabilized with formalin, and preserved with 0.01% thimerosal (mercury derivative). The vaccine contains not more than 1:12,000 formalin, used during the process. It does not contain penicillin. Aluminum phosphate, 1.5 mg. per 0.5 ml. is added to the vaccine as an adjuvant. **Indications:** FLUOGEN is indicated for the production of immunity to influenza produced by the strains of virus containing antigens related to those in the vaccine. FLUOGEN is recommended primarily as a seasonal booster for persons who were previously vaccinated with vaccines containing the A_2 Hong Kong variant. It may also be used for primary immunization of those who have not previously received the Hong Kong variant. It is recommended that both primary and booster immunization be completed by early December since influenza is more likely to appear during cold weather. It is understood that should epidemic conditions be predicted, immunization procedures should be initiated regardless of the time of year. Attempts to produce immunity following the appearance of an epidemic may be less successful because of the rapidity with which the disease spreads and the time required for antibody production following vaccination. The degree of protection afforded by immunization with any vaccine may not be sufficient to prevent the disease if the exposure to the influenza virus strains is overwhelming or if the virus strains are not closely related antigenically to those used in the production of vaccine. Although routine vaccination of healthy groups of adults and children is not recommended, when widespread epidemics of influenza are forecast, vaccination may be considered if above-average levels of absenteeism would disrupt satisfactory operations in industries, schools, and other such groups. **Contraindications:** The use of products prepared from the embryonic fluid of chicken eggs is contraindicated in persons with a history of allergy to eggs, chicken, chicken feathers, or chicken dander. In persons suspected of having an allergic condition, immunization procedures should be preceded by a scratch test or an intradermal injection (0.05 ml. to 0.1 ml.) of vaccine diluted 1:100 in sterile saline to determine possible sensitivity to the minute residual egg protein that may be present in the vaccine. A positive skin reaction contraindicates immunization with the vaccine. Immunization should be deferred in the presence of any acute respiratory disease or other active infection. It should also be deferred in the presence of an epidemic of poliomyelitis unless the risk of influenza represents a greater threat to the patient than the increased possibility of poliomyelitis. **Precautions:** A separate sterile syringe and needle should be used for each patient to prevent transmission of homologous serum hepatitis virus or other infectious agent from one person to another. Reusable glass syringes and needles should be heat sterilized. Epinephrine should be immediately available for use should an acute anaphylactoid reaction occur in individuals having an undisclosed hypersensitivity to any component of the vaccine. Because of the possibility of a febrile reaction following immunization with influenza virus vaccine, the wisdom of attempting to immunize patients with a history of febrile convulsion should be given careful consideration. **Adverse reactions:** Most frequent reaction reported in early clinical studies[†] with ether-extracted vaccine was tenderness at the site of injection. Headache and malaise were reported in up to about 12% of subjects. Nausea and fever occurred in approximately 5% of the patients. Muscle ache, joint pain, chills, fatigue, and anorexia occurred in less than 5% of the subjects. **Package information:** Bio 579—5 cc. rubber-diaphragm-capped vial. Each 5 cc. vial contains sufficient vaccine to deliver ten 0.5 cc. doses.

[†] Unpublished data available upon request.

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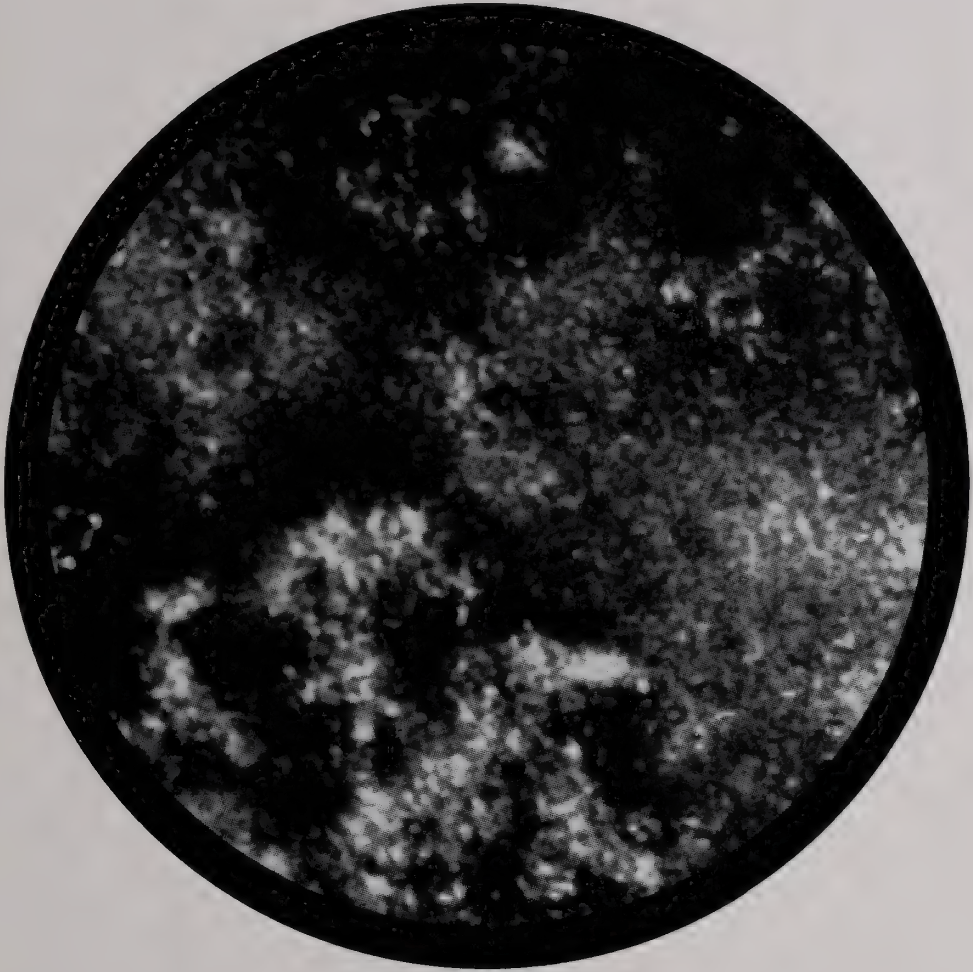
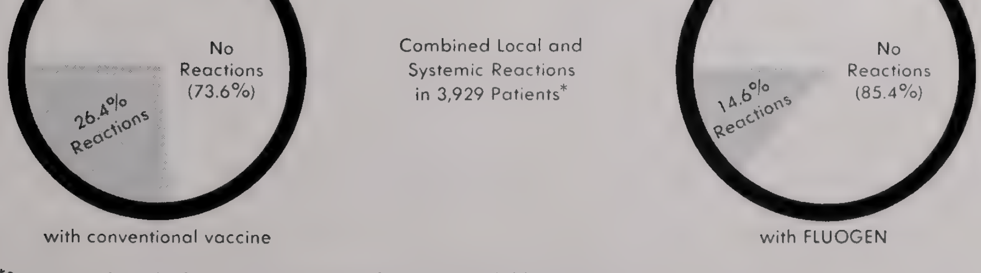
we had to take our conventional flu vaccine two steps beyond "purified" to make it look like this...



...and cut its side effects almost in half



*Summary of results from three studies. References available on request.

Convalescing . . . but still a long way to go. Anxiety can make it even longer.

Convalescence following medical or surgical procedures may be almost endless to an anxious patient. And, indeed, anxiety with some patients actually retards progress—for example, by inducing insomnia and reducing cooperation.

As physicians have found during nearly 15 years of widespread use, Equanil may be a beneficial part of aftercare. It helps relieve anxiety and tension, thus often aiding your primary therapy.

Indications: For use in management of anxiety and tension occurring alone or as accompanying symptom complex to medical and surgical disorders and procedures. Though not a hypnotic, fosters normal sleep through antianxiety and related muscle-relaxant properties.

Contraindications: History of sensitivity to meprobamate.

Important Precautions: Carefully supervise dose and amounts prescribed, especially for patients prone to overdose themselves. Excessive prolonged use has been reported to result in dependence or habituation in susceptible persons, as alcoholics, ex-addicts, and other severe psychoneurotics. After prolonged excessive dosage, reduce dosage gradually to avoid possibly severe withdrawal reactions. Abrupt discontinuance of excessive doses has sometimes resulted in epileptiform seizures.

Warn patients of possible reduced alcohol tolerance, with resultant slowing of reaction time and impairment of judgment and coordination.

Reduce dose if drowsiness, ataxia or visual disturbance occurs; if persistent, patients should not operate vehicles or dangerous machinery.

Side Effects include drowsiness, usually transient; if persistent and associated with ataxia, usually responds to dose reduction; occasionally concomitant CNS stimulants (amphetamine, mephentermine sulfate) are desirable. Allergic or idiosyncratic reactions are rare, but such reactions, sometimes severe, can develop in patients receiving only 1 to 4 doses who have had no previous contact with meprobamate. Previous history of allergy may or may not be related to incidence of reactions. Mild reactions are characterized by itchy urticarial or erythematous maculopapular rash, generalized or confined to groin. Acute nonthrombocytopenic purpura with cutaneous petechiae, ecchymoses, peripheral edema and fever have been reported. One fatal case of bullous dermatitis following intermittent use of meprobamate with prednisolone has been reported. If allergic reaction occurs, meprobamate should be stopped and not reinstituted. Severe reactions, observed very rarely, include angioneurotic edema, bronchial spasms, fever, fainting spells, hypotensive crises (1 fatal case), anaphylaxis, stomatitis and proctitis (1 case) and hyperthermia. Treat symptomatically as with epinephrine, antihistamine and possibly hydrocortisone. Aplastic anemia (1 fatal case), thrombocytopenic purpura, agranulocytosis and hemolytic anemia have occurred rarely, almost always in presence of known toxic agents. A few cases of leukopenia, usually transient, have been reported on continuous administration.

Meprobamate may sometimes precipitate grand mal attacks in patients susceptible to both grand and petit mal. Extremely large doses can produce rhythmic fast activity in the cortical pattern. Impairment of accommodation and visual acuity has been reported rarely. After excessive dosage for weeks or months, withdraw gradually (1 or 2 weeks) to avoid recurrence of pretreatment symptoms (insomnia, severe anxiety, anorexia). Abrupt discontinuance of excessive doses has sometimes resulted in vomiting, ataxia, tremors, muscle twitching and epileptiform seizures. Prescribe very cautiously and in small amounts for patients with suicidal tendencies. Suicidal attempts have resulted in coma, shock, vasomotor and respiratory collapse and anuria. Excessive doses have resulted in prompt sleep; reduction of blood pressure, pulse and respiratory rates to basal levels; and occasionally hyperventilation. Treat with immediate gastric lavage and appropriate symptomatic therapy. (CNS stimulants and pressor amines as indicated.) Doses above 2400 mg./day are not recommended.

Composition: Tablets, 200 mg. and 400 mg. meprobamate. Coated Tablets, WYSEALS® EQUANIL (meprobamate) 400 mg. (All tablets also available in REDIPAK® [strip pack], Wyeth.) Continuous-Release Capsules, EQUANIL L-A (meprobamate) 400 mg.

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Indications: Tybatran (tybamate) has afforded symptomatic improvement in a variety of psychoneurotic disorders, especially in the treatment of the anxiety and tension components of psychoneuroses. Anxiety states manifested somatically have responded to Tybatran (tybamate).

Tybatran (tybamate) has been useful in the control of agitation in the aged and in the alleviation of some of the adverse emotional accompaniments of senility.

Tybatran (tybamate) has been used with benefit in the treatment of depressive symptoms associated with anxiety and other symptoms of psychoneuroses. However, it is not indicated for primary treatment of depressive states. It is not an antipsychotic agent, although it has been used as adjunctive therapy in some psychotic patients.

Dosage: One 350 mg. capsule, 3 times daily and two at bedtime is suggested as the adult starting dose. Adjust to suit individual requirements. Daily doses above 3000 mg. are not recommended.

Contraindications: Known hypersensitivity to tybamate. Since no studies have been done with this drug in human pregnancy, it should not be used in pregnancy unless the potential benefit outweighs the risk.

Warnings: Administer cautiously to patients receiving phenothiazines or other CNS depressants or having history of convulsive seizures (See Adverse Reactions). Consider possibility of additive actions with alcohol or other psychotropic agents, particularly phenothiazines or MAO inhibitors.

Precautions: Avoid abrupt withdrawal after prolonged use, although withdrawal symptoms have not been reported to date. Exercise caution in addiction-prone individuals. If symptoms of hypersensitivity occur, discontinue at once and initiate appropriate symptomatic treatment. Avoid activities requiring optimal mental alertness if drowsiness or vertigo are present. As with any new drug, use cautiously in patients with history of drug allergies, blood dyscrasias, and hepatic or renal disease; periodic measurements of hepatic, hematopoietic and renal function should accompany prolonged and/or high doses.

Adverse Reactions: Most frequent reactions, rarely requiring discontinuation of tybamate, include drowsiness, dizziness, nausea, insomnia, and euphoria. There have been a few reports of skin rash, urticaria, and pruritus. Rare side effects include hyperactivity, fidgetiness, flushing, and tachycardia, suggesting excessive stimulation; also ataxia, unsteadiness, confusion, feeling of unreality, "panic reaction," fatigue, headache, paresthesias, vertigo, gastrointestinal disturbances, glossitis, and dry mouth. Grand mal or petit mal seizures have been reported in a few hospitalized psychotic patients receiving tybamate (up to 6000 mg. daily) together with phenothiazines and other psychotropic agents, but not with tybamate alone. Consider the possibility of rare, serious adverse reactions such as may occur with the related drug, meprobamate. If excessive amounts are ingested, gastric lavage and symptomatic therapy, including central stimulants as necessary, are recommended. Before prescribing, consult package circular.

Supply: Tybatran (tybamate) is available in green, sealed capsules of three strengths: 350 mg., 250 mg., and 125 mg. Each strength is supplied in bottles of 100 and 500.

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Contraindications: Concurrently with MAO inhibitors, in patients hypersensitive to this drug; in emotionally unstable patients susceptible to drug abuse.

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As is characteristic of sympathomimetic agents, it may occasionally cause *CNS effects* such as insomnia, nervousness, dizziness, anxiety, and jitteriness. In contrast, CNS depression has been reported. In a few epileptics an increase in convulsive episodes has been reported.

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Allergic phenomena reported include such conditions as rash, urticaria, ecchymosis, and erythema.

Gastrointestinal effects such as diarrhea, constipation, nausea, vomiting, and abdominal discomfort have been reported.

Specific reports on the hematopoietic system include two each of bone marrow depression, agranulocytosis, and leukopenia.

A variety of miscellaneous adverse reactions have been reported by physicians. These include complaints such as dry mouth, headache, dyspnea, menstrual upset, hair loss, muscle pain, decreased libido, dysuria, and polyuria.

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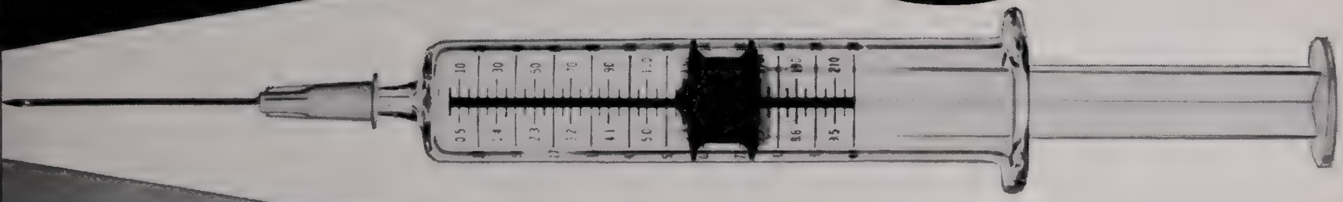

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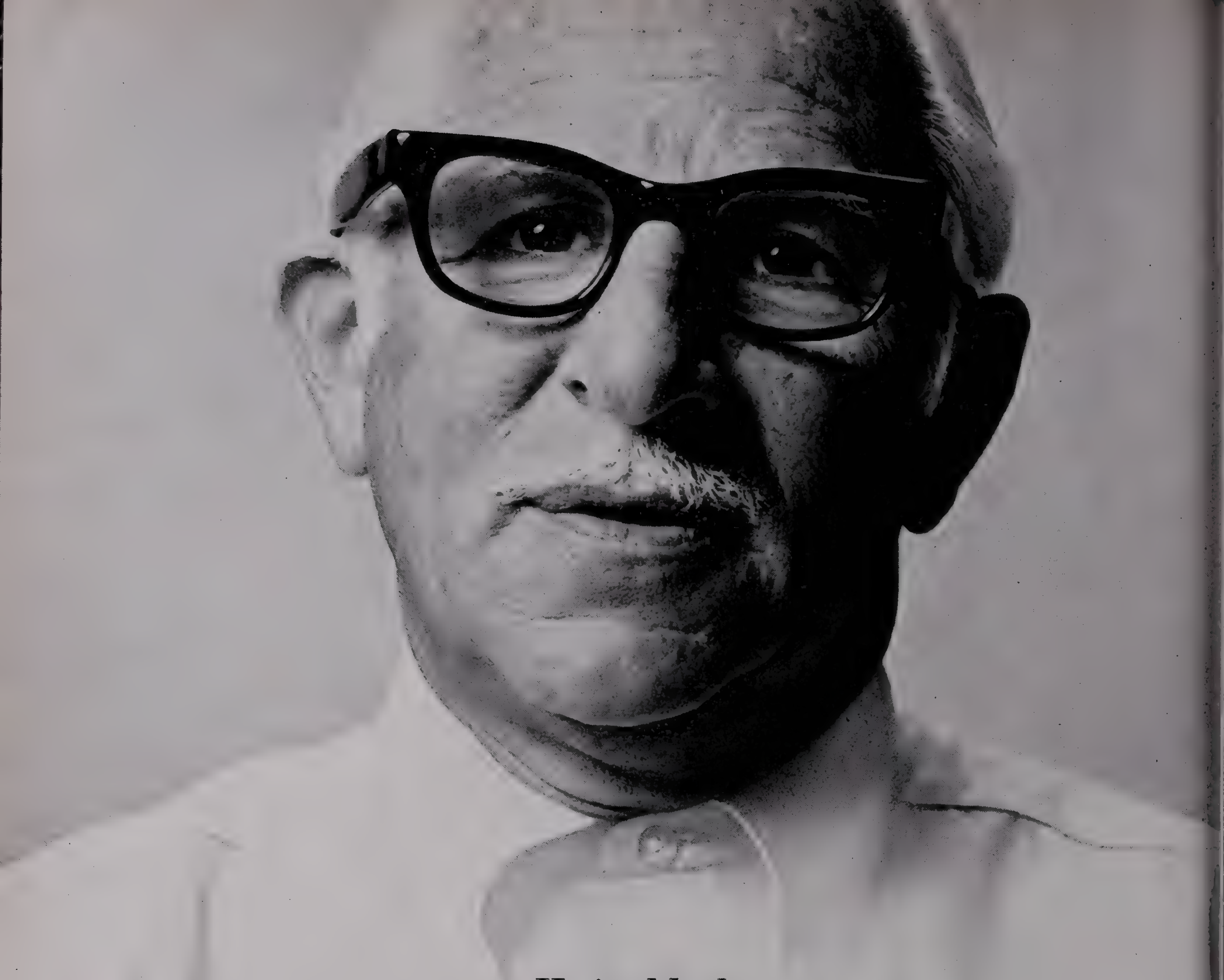

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For your susceptible candidates, prescribe DECLOSTATIN—the broad-spectrum therapy that prevents monilial overgrowth.

Contraindication: History of hypersensitivity to demethylchlortetracycline or nystatin.

Warning: In renal impairment, usual doses may lead to excessive accumulation and liver toxicity. Under such conditions, lower than usual doses are indicated, and, if therapy is prolonged, serum level determinations may be advisable. A photodynamic reaction to natural or artificial sunlight has been observed. Small amounts of drug and short exposure may produce an exaggerated sunburn reaction which may range from erythema to severe skin manifestations. In a smaller proportion, photoallergic reactions have been reported. Patients should avoid direct exposure to sunlight and discontinue drug at the first evidence of skin discomfort. Necessary subsequent courses of treatment with tetracyclines should be carefully observed.

Precautions: Overgrowth of nonsusceptible organisms may occur. Constant observation is essential. If new infections appear, appropri
measures should be taken.

In infants, increased intracranial pressure with bulging fontanels
been observed. All signs and symptoms have disappeared rapidly u
cessation of treatment.

Side Effects: Gastrointestinal system—anorexia, nausea, vomiting, di
rhea, stomatitis, glossitis, enterocolitis, pruritus ani. Skin—maculop
ular and erythematous rashes; a rare case of exfoliative dermatitis
been reported. Photosensitivity; onycholysis and discoloration of
nails (rare). Kidney—rise in BUN, apparently dose related. Transi
increase in urinary output, sometimes accompanied by thirst (rar
Hypersensitivity reactions—urticaria, angioneurotic edema, anaphyla
Teeth—dental staining (yellow-brown) in children of mothers given
drug during the latter half of pregnancy, and in children given the d
during the neonatal period, infancy and early childhood. Enamel hy
plasia has been seen in a few children. If adverse reaction or idios
crasy occurs, discontinue medication and institute appropriate thera
Average Adult Daily Dosage: 150 mg q.i.d. or 300 mg b.i.d. Should
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by the concomitant administration of high calcium content drugs, f
and some dairy products. Treatment of streptococcal infections sh
continue for 10 days, even though symptoms have subsided.

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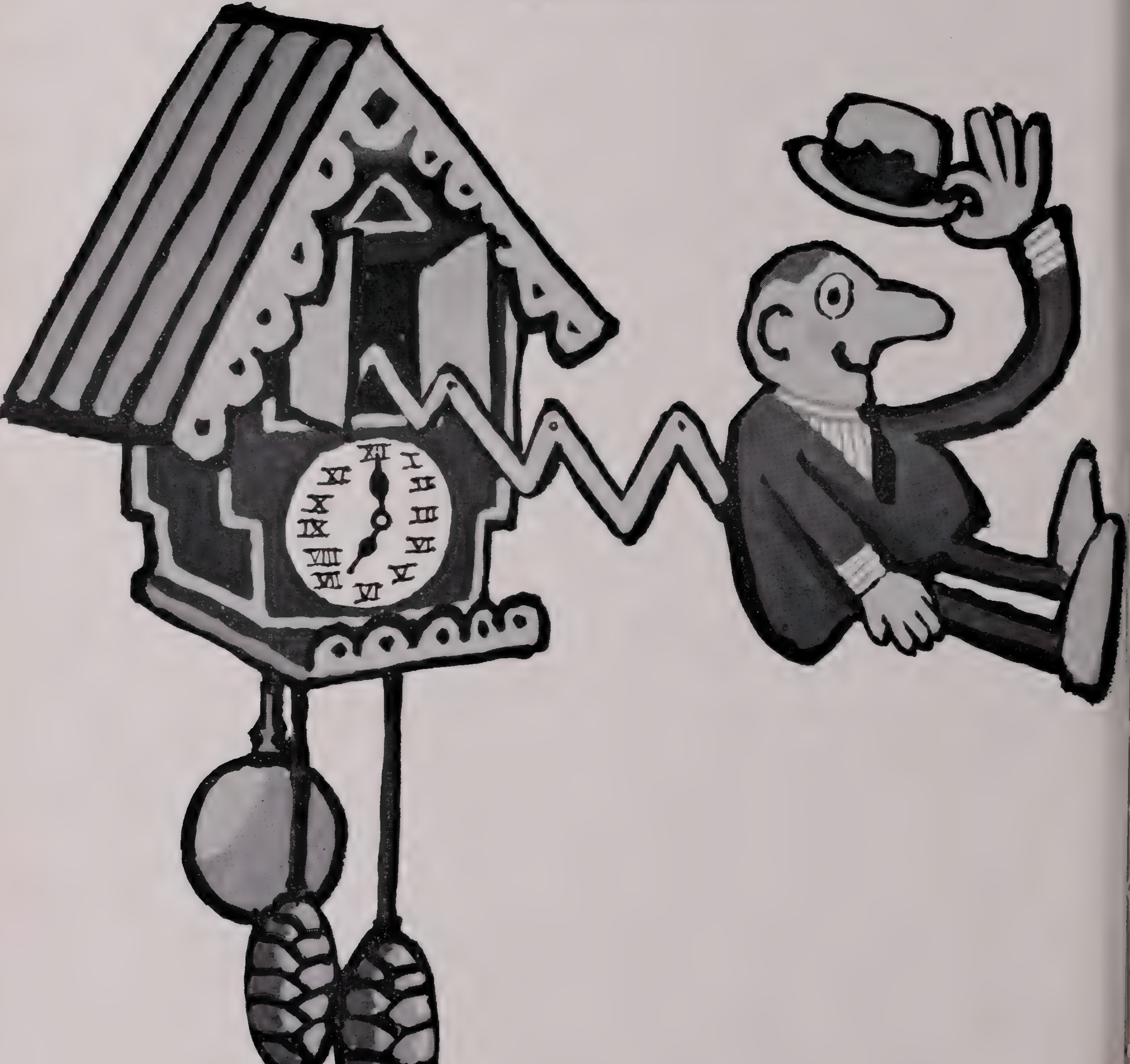

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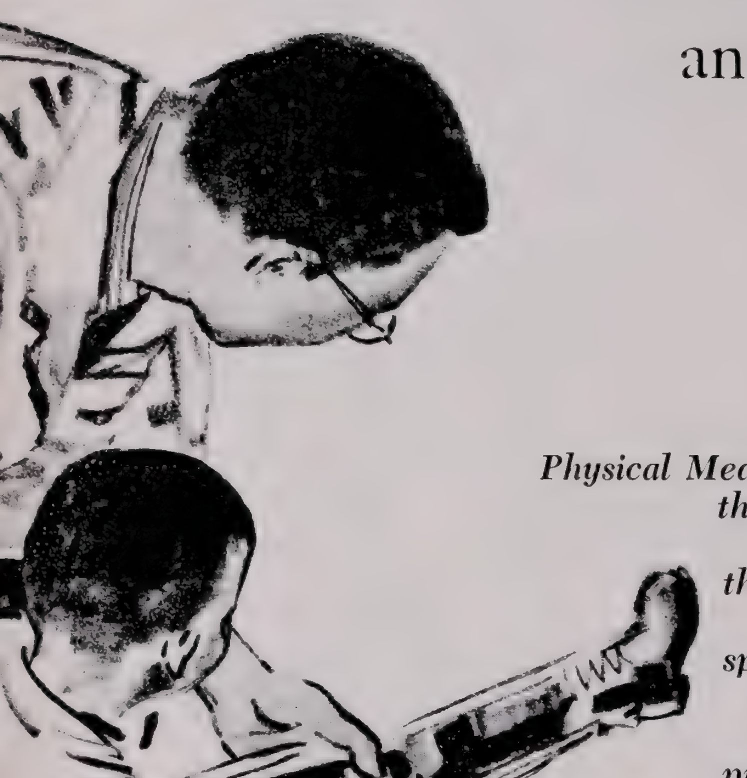

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Chairman's Letter

Chronic Respiratory Disease in Children

THE EXTENT TO which chronic respiratory diseases cripple children was reported in three recent United States surveys. The first, July '59-61, concluded that one of every ten children was handicapped by asthma, bronchitis, bronchiectasis, cystic fibrosis, emphysema, or congenital pulmonary disorders. These conditions caused almost half of all childhood chronic diseases.

The second survey, July '61-63, found that over 50 percent of persons handicapped by respiratory diseases were confined to bed for one or more days, 11 percent for more than thirty days.

The third survey, July '63-65, showed that these chronic respiratory conditions caused 13 percent of all disability under age 45.

Furthermore, these diseases caused 10 percent of the deaths in persons under 20 years of age (Vital Statistics U.S., 1966).

The apparent mildness of the early symptoms of pathology in these diseases, i.e., cough or tachypnea (Waring and Harries)* are often slighted by patients, parents, and physicians who thereby miss the opportunity for preventive treatment (Waring).*

Even, if the symptoms are appreciated, the need for special treatments and for long-term frequent observations in order to control or prevent progression of the disease (Matthews and Doershuk)* is frequently not appreciated.

The long-term work in this field by the National Cystic Fibrosis Research Foundation has recently encouraged the Congress to fund Pediatric Pulmonary Centers under two Federal Programs (Herndon).*

The combination of voluntary health agencies and the Federal Government should do much to solve the problems of inadequate facilities and funds (1) for care of children with these diseases (2) for research into their pathogenesis and (3) for educational programs for physicians and paramedical personnel.

The treatment techniques which have improved the prognosis for cystic fibrosis (Pogue and Warwick)* have been shown to be similarly effective for many children with other chronic respiratory problems. While specific therapy for all these diseases will depend upon discovery of the basic abnormalities, clinical and basic studies of the mechanisms of and recovery from lung damage, of susceptibility and resistance to infections, and of pulmonary function in health and disease will make it possible to slow down, control, or even reverse pulmonary damage in these diseases.

The magnitude of the chronic respiratory disease problem in children and adolescents (Kendig)* emphasizes the need for expansion of effort, manpower, training and research into diagnosis, care, and prevention and the smallness of the resources available to expand manpower, training, and research.

Funds have been available to exert a direct influence on cystic fibrosis. That effort ought to be considered a pilot study on a severe chronic pediatric pulmonary disease, and an example of how to proceed on the greater problems.

Warren J. Warwick, M.D.†
Chairman, Medical Care Committee
National Cystic Fibrosis Research Foundation

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*This issue of Minnesota Medicine.
†Vice-President, Cystic Fibrosis Club.

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STATE MEDICAL ASSOCIATION

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Number 9

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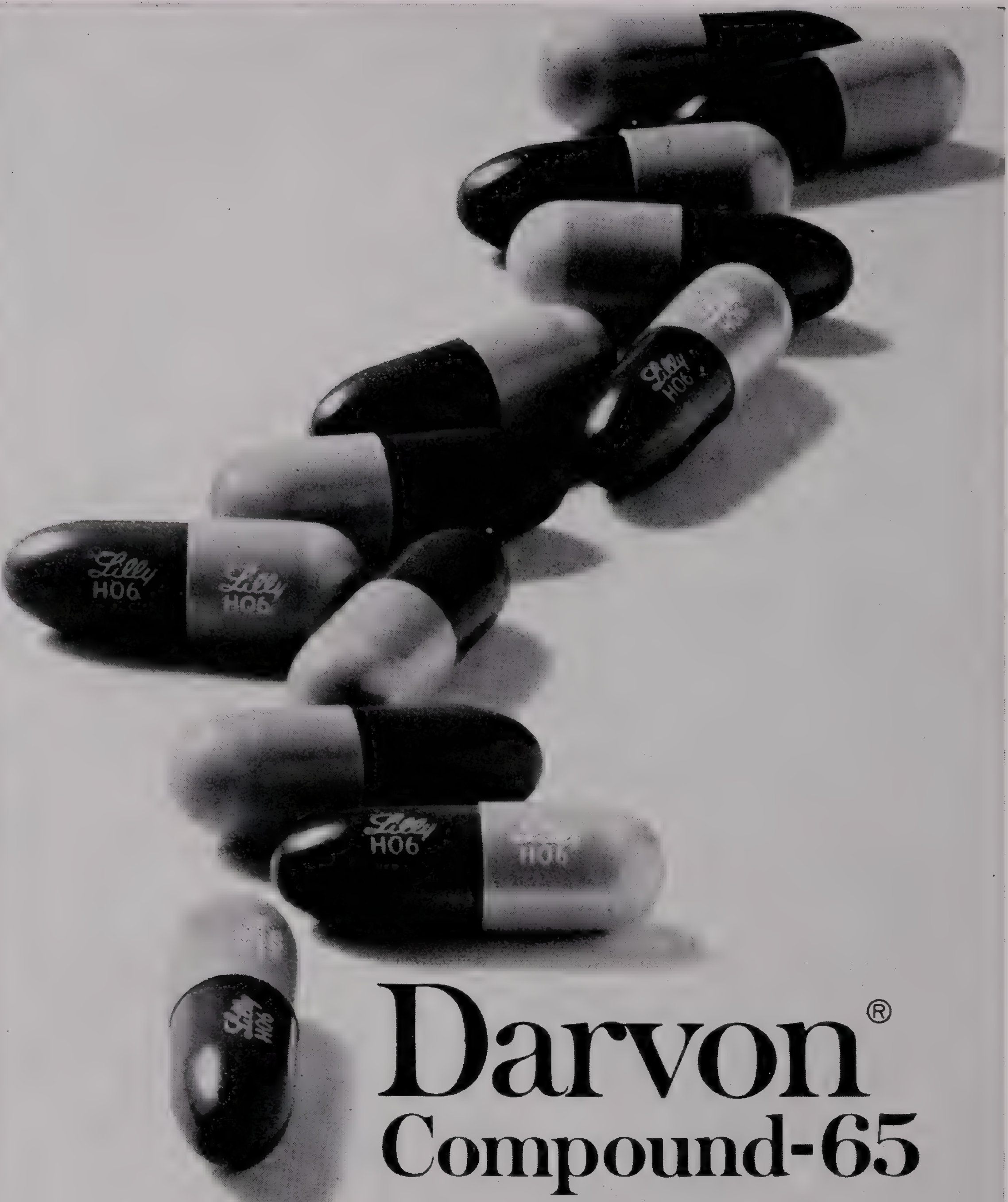

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Chronic Respiratory Diseases in Children*

EDWIN L. KENDIG, JR., M.D.†
Richmond, Virginia

THE STUDY of the unglamorous chronic respiratory disease in children has lagged behind that in other pediatric subspecialties during recent years. Endocrinology, cardiology, the study of inborn errors of metabolism and developmental problems have all at one time or another been the glamour field for pediatricians.

There has, however, been a great change in the past 30 years. In 1938 cystic fibrosis was considered a rare pancreatic disorder, uniformly fatal and affecting only a small number of infants; no specific antimicrobial agents were available for the treatment of tuberculosis; and the unclassified mycobacteria were thought to be harmless saprophytes. Sarcoidosis was a rare disease indeed and histoplasmosis was considered a systemic fungous disease which was uniformly fatal. Bronchogenic carcinoma was not a major problem and cigarette smoking as a cause had not been suspected. Pulmonary function in children was a field barely touched.

A partial listing of chronic respiratory diseases and problem areas of the present day might be catalogued as follows:

(1) Hyaline Membrane Disease; (2) Bronchial Asthma; (3) Cystic Fibrosis; (4) Atelectasis; (5) Bronchiectasis; (6) Tuberculosis; (7) Systemic Mycoses; (8) Infection with the Unclassified Mycobacteria; (9) Sarcoidosis; (10) Familial Dysautonomia; (11) Histiocytosis X; (12) Collagen Diseases; (13) Visceral Larva Migrans; (14) Loeffler's Syndrome; (15) Psittacosis; (16) Hemosiderosis; (17) Idiopathic Diffuse Interstitial Fibrosis (Hamman-Rich); (18) Pulmonary Alveolar Proteinosis; (19) Alveolar Microlithiasis; (20) Bronchogenic Carcinoma; (21) Chronic Granulomatosis.

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*Read at the Regional Continuation Course on Chronic Respiratory Diseases in Children and Adolescents at the University of Minnesota, Minneapolis, September 17, 1968.

†Department of Pediatrics, Medical College of Virginia, Health Sciences Division, Virginia Commonwealth University, Director of Child Chest Clinic, Medical College of Virginia Hospitals, Richmond, Virginia.

Hyaline Membrane Disease

Hyaline membrane disease, the respiratory distress syndrome usually occurring in premature infants, was first described more than 60 years ago. However, it is only in the past 15 years that the subject has attracted such great interest and, while much knowledge has been gained, there is still no completely endorsed treatment. The most common approach is directed toward the correction of the metabolic and respiratory acidosis. However, recent evidence that there may be severe lung damage associated with a prolonged use of high concentrations of oxygen and respirator therapy has prompted some investigators to alter their treatment of hyaline membrane disease.[1]

Cystic Fibrosis

Many things have been learned about cystic fibrosis during the past 30 years. Shwachman has summarized them as follows: "Cystic fibrosis is not a disease limited to the pancreas, but is an involvement of the exocrine glands; it is not a rare disease, occurring 10 to 20 times as frequently as does phenylketonuria; survival into adulthood and even parenthood can be achieved; the diagnosis can be made with ease, even in the neonatal period; it is a hereditary disease transmitted as a mendelian recessive; it is a serious disease affecting the respiratory system in nearly all cases; and the cause of death is most often related to the pulmonary involvement."

Improved Prognosis

Doershuk and Matthews[7] credit five advances for the improved prognosis in this disease: (1) development of dietary and pancreatic enzyme replacement therapy[12]; (2) control of the secondary bacterial pulmonary infection with antibiotics[12]; (3) early and more definitive diagnosis utilizing the sweat test[13]; (4) control of the primary obstructive pulmonary lesion[14], and (5) early institution of prophylactic therapy aimed at preventing pulmonary involvement.[15]

The nature of the basic disorder is unknown and therapy must, therefore, be nonspecific and aimed at the relief of the presenting complaints and prevention of complications. Determination of the cause of this disease is of paramount importance.

Bronchial Asthma

Twenty-two percent of all days lost from school because of chronic conditions was due to asthma. According to Dees, 1.5 million children have asthma.[2]

Antibody Selectivity

This crippling disease has been treated by hyposensitization for more than 50 years, and it is thought that such injections stimulate the production of an antibody different from the spontaneously occurring skin-sensitizing "reagin;" this antibody selectively shows greater affinity for the allergen than does the reagin present in the sensitized shock organ or cell. It has, therefore, been postulated that antigen-antibody union is consummated by the "blocking" antibody, thereby protecting cells from the damage caused by the mediators of an allergic reaction which would otherwise have taken place in some vulnerable tissue such as the bronchial tree or the lungs.[2] There are, however, many experimental and clinical observations which cannot be reconciled with this oversimplified explanation.

More recent postulates suggest that hyposensitization produces partial acquired tolerance, or immunological unresponsiveness, to some components of the antigen. This may explain decreased symptoms upon exposure to allergens and smaller degrees of specific skin reactivity. Other antigenic components appear to induce immunity as shown by rise in titer of blocking and hemagglutinating antibodies.[3]

Imbalance of Adrenergic Receptors

In certain instances, too, bacteria or their products may effect a lowered threshold to bronchospasm or altered reactivity to mediators induced by an imbalance of the adrenergic receptors of the autonomic nervous system.[4]

It has been suggested that sudden death from asthma has increased as a result of the widespread use of corticosteroid medication. In addition to the controversial effects of steroids, there has been excessive use of aerosolized sympathomimetics. The interaction of isoproteronol and the simultaneous administration of sedatives and tranquilizers leading to a "locked lung syndrome" has been reported. Early recognition of this potentially fatal condition and intervention to discontinue aerosol medication may prevent sudden death in asthma.[5]

Further study also is indicated to determine why emotional stress should be a major trigger factor in so many instances.

Pulmonary Hemosiderosis

Chronic pulmonary disease associated with serum precipitating antibodies to milk has been reported by Heiner.[6] Features of the syndrome include recurrent migratory pneumonitis, hemoptysis, iron-laden macrophages in gastric washings, sputum or lung aspirate, iron deficiency anemia, gastrointestinal symptoms and growth failure. This form of pulmonary hemosiderosis responds to withdrawal of milk from the diet.

Atelectasis

Atelectasis may arise under a variety of circumstances: (1) bronchial obstruction, either (A) extrabronchial or (B) intrabronchial, endogenous or exogeneous; (2) abnormal alveolar surface tension; (3) direct local pressure on parenchymal tissue; (4) increased intrapleural pressure; (5) neuromuscular pathology.

Etiology

Perhaps the most important cause of atelectasis is endogenous intrabronchial obstruction. This may originate within the bronchus as granulomatous tissue, most often tuberculous in origin, or mucous material, frequently secondary to cystic fibrosis or asthma.

The course and duration of such atelectasis in children depend on many factors, most important of which is the physiologic state of the obstructed bronchus. In asthmatic patients the smooth muscle spasm promotes narrowing of the lumen and facilitates obstruction. Effective medication may quickly restore the lumen to almost normal diameter. On the other hand, in bronchopneumonia, bronchiolitis, and cystic fibrosis, the inherent disease of the bronchi manifested by both edema and swelling, within the bronchi, peribronchial exudate, and the mucoid material filling the bronchus favor obstruction at various areas which, when relieved in one area, may appear in another as long as the infection thrives.[19]

The chronicity of the infection which results in damage to bronchi, and the sort of material obstructing the lumen of the bronchus also determine the outcome of the atelectasis.[19]

Bronchiectasis

It is now generally agreed that infection and obstruction of the bronchi are the two important etiologic factors in the production of acquired bronchiectasis. It is also clear that mechanical stress and obstruction alone may not result in permanent damage to the bronchi.

Tuberculosis

The mortality from tuberculosis has been markedly reduced in recent years, from 200 per 100,000 population in 1900 to less than 50 in 1940, and to only 4.9 per 100,000 in 1963.

Antituberculosis Agents

Undoubtedly, better case finding and improved living conditions have been major factors, and the advent of streptomycin in 1944 and isoniazid in 1952 has resulted in an even more precipitate drop. More recently ethionamide and now ethambutol have shown indications of being effective antituberculosis chemotherapeutic agents.

However, the new measure of the seriousness of tuberculosis is the number of new active cases; in 1962 there were 53,315 reported cases in the U.S., a figure which included an estimated 10,000 relapses. More than 11 percent of the cases reported in 1962 were in individuals less than 14 years of age.

That tuberculosis can be controlled solely by antimicrobial agents seems extremely doubtful. Certainly this cannot be accomplished with the drugs now available. There is, therefore, need for a better antituberculosis chemotherapeutic agent and either better case-finding-methods, or a more effective use of the tools now available.

Systemic Mycoses

Since 1957 amphotericin B has been used in the treatment of virtually all of the true *systemic mycoses.* However, this drug is pyrogenic, producing chills and high fever, is poorly absorbed from the gastrointestinal tract and is both hepatotoxic and nephrotoxic. The renal toxicity is dose-related and, in the vast majority of patients, irreversible. This toxicity has warranted a continuing search for newer agents. The first of these, saramycetin, a polypeptide which is administered subcutaneously, has produced marked reversal of clinical disease and cultural results in patients with histoplasmosis, blastomycosis, sporotrichosis, and aspergillosis. A study project using this drug in the treatment of chronic cavitary histoplasmosis is now in progress. A second drug, hamycin, a polyene closely resembling amphotericin B, is especially attractive since it appears to be better absorbed by the gastrointestinal route and has shown chemotherapeutic activity and virtually no toxicity in patients with blastomycosis and histoplasmosis. The most recent drug is 5-fluorocytosine, another drug for oral administration, which has been demonstrated to be chemotherapeutically active in experimental cryptococcosis and candidiasis in mice. These three agents[20] presage an era when there may be far greater choice in the treatment of the systemic mycoses in man.

Unclassified Mycobacteria

In recent years it has been established by examination of resected pulmonary lesions and suppurative lymph nodes that human disease can be caused by mycobacteria previously considered to be harmless. These pathogenic organisms are called unclassified (anonymous, atypical) mycobacteria and may be the cause of pulmonary disease resembling tuberculosis in adults and chronic suppurative lymphadenitis, particularly in children.

It is not yet completely settled whether or not these organisms may be mutations of M. tuberculosis treated with antituberculosis drugs, but the fact that many acid-fast organisms exist in nature, and existed for many years before the advent of the antituberculosis chemotherapeutic agents, indicates that this is, at best, not the complete answer.

Excision of Lymph Nodes

Prompt excision of the suppurative lymph nodes is the most important part of the therapeutic approach. In those patients with pulmonary disease who have localized lesions which have not responded to chemotherapy and who are in satisfactory general condition, resection is the treatment of choice as there is no satisfactory chemotherapeutic agent available for treatment of these infections.

Dysautonomia

Familial dysautonomia is a rare disease, and the diagnosis is still a clinical one. No satisfactory pathologic basis has been established. The recurrent pulmonary lesions are probably the result of a defective swallowing mechanism with associated aspiration. Treatment is supportive and symptomatic; no specific therapy is available.

Collagen Diseases

Among the collagen diseases the incidence of pulmonary involvement is relatively frequent and such lesions may be grouped as follows: (1) Inflammation of the pleura or pericardium. This may be either fibrinous or effusive and in Still's disease is a more common finding than is parenchymal involvement. The demonstration of a lupus erythematosus cell, in pleural fluid, is pathognomonic of that disease. In adult rheumatoid arthritis the rheumatoid factor may be present in the pleural or pericardial fluid, but in a child so affected it is not likely to be found. (2) In the lung parenchyma, fibrosis is the most common finding and closely resembles the Hamman-Rich syndrome* in histology and pathophysiologic function. The most serious and extensive fibrosis may be found in scleroderma. A distinctive disc type of atelectasis in the lung base is sometimes present in lupus erythematosus. A granulomatous lesion, seen more often in adult rheumatoid arthritis, is not as likely to occur in children. (3) Involvement of the vascular bed of the lung has begun to attract more attention. The extent of damage may range from mild fibrosis to complete necrosis and occlusion. Pulmonary hypertension and right side heart failure may result. Also, disturbed pulmonary function has been described in systemic lupus erythematosus with little or no evidence of parenchymal disease. This is presumably due to vascular disease.

Bronchogenic Carcinoma

The most highly publicized respiratory disease today, bronchogenic carcinoma, is not, strictly speaking, a major problem in children. It has, however, become increasingly common in adult life and cigarette smoking has apparently been implicated as either a major causative factor, or, at the very least, a contributing one in this usually fatal malady.

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*See Page 1372.

The cigarette-smoking teenager is embarking on a habit which may culminate in bronchogenic carcinoma, emphysema, or other lung or cardiac disturbance which will, on an average, reduce his or her life expectancy four to eight years. According to a recent Public Health survey, smoking among teenagers has declined appreciably over the past 10 years: however, it is not decreasing fast enough and each day more than 3,000 youngsters take up smoking.

More research in this important area is undoubtedly necessary but, with the knowledge at hand, it is incumbent on all practitioners of pediatrics to make every effort to influence the adolescent to refrain from smoking.

It has been suggested that this can be accomplished in three ways: the pediatrician can approach the problem through the child's parents, through the child himself, and by his own example, i.e., not smoking himself and asking staff and visitors not to smoke in his office or waiting room.

Concluding Comments

Air pollution as the cause of emphysema and other pulmonary disease also needs further study; beneficial influence toward the correction of this problem may also be furnished by the pediatric practitioner.

The field of chronic pulmonary disease in children has changed considerably from 1938 to 1968; and it is apparent from this partial listing that progress has been great. One of the more recent advances has been in the field of pulmonary function.[21] However, the number of medical centers in which there is satisfactory equipment and skill for the study of pulmonary function in infants and young children is small, and, indeed, the presently-used studies for infants and young children must be simplified and thus rendered more available.

Chronic respiratory disease in children has changed. Many problems, not even recognized a few years ago, have already been solved; however, as is often the case, progress has merely resulted in the demonstration of other problems, to date unsolved. There is yet a long way to go.

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10-21. May be found on page 1573.

Man

If we eliminated all the unfilled space in a man's body and collected his protons and electrons into one mass, the man would be reduced to a speck just visible with a magnifying glass.—Professor Arthur Eddington

FEATURE SPECIAL

Old Hospitals

Epidauros

Epidauros is located on the Peloponnesus about a hundred miles drive west of Athens. Historically it is an important landmark among institutions of healing because it witnessed a transition from pre-Hellenic faith healing to the rational and vaguely scientific system that was ancient Greek medicine. At Epidauros was the most celebrated temple of the God of Medicine, Asclepios, and its practitioners were priests. The priests recognized, however, that some diseases were purely organic, and apparently made frequent referrals to the physicians whose schools were located nearby.

Ruins of the Abaton at Epidauros

The temple was the center of a complex which included a sports stadium, places for musical performances, and a theatre (still in use) seating 14,000. These diversions and the pleasant surroundings of the Greek countryside prepared the patients for the drug-induced narcosynthesis and suggestion therapy practiced by the priests. The drugs were administered in a large building adjacent to the temple and called the abaton. The ruins of the abaton at Epidauros are pictured above. The building was lined with couches where the patients reclined during their diagnostic and therapeutic sessions.

While the practices of the priests anticipated modern psychiatry and psychosomatic medicine, the over-all function of the health complex is more reminiscent of a sanitarium or spa than of a hospital.

Warren Kump, M.D.
Minneapolis, Minnesota

Ann Med Hist N.S. III, 501, 1931.

Health Effects from Exposure to Air Pollutants*

HAROLD J. PAULUS, Ph.D.†
Minneapolis, Minnesota

ONE OF THE MOST important items in our environment is the envelope of air in which we live. Until a few decades ago this necessary commodity was taken for granted. Man, in his quest for wealth and his desire to do things the easy way, has sorely abused the layer of air nearest the earth. Today we see a steadily increasing problem throughout the country, even throughout the world: air pollution.

It is small wonder that the most serious result of air pollution would be its effect on the respiratory system: mainly the lungs.

Air Pollutants

The Concentration

The concentration in the outdoor air of specific gaseous air pollutants is presently in the low parts per million range. As an example, sulfur dioxide is recorded as below 0.1 part per million by volume for greater than 95% of the time in the Twin Cities; but carbon monoxide with an average of about 35 parts per million for an hour or longer on the streets of Minneapolis and St. Paul under certain weather conditions may constitute cause for concern.

The Composition

Air pollutants are generally classified as particulates and gases. The *particulates* include dusts which may be both naturally occurring and man-made: fumes, smoke and mist. Dust particles may be chemically classified as carbonaceous, containing combustible carbon; silicious, having free silica or silicates in the compound, or of a specific chemical composition such as cement dust.

The most common *gaseous air pollutants* are the sulfur gases including sulfur dioxide, hydrogen sulfide, a series of thiols and mercaptans; the nitrogen gases consisting mainly of oxides of nitrogen and ammonia, ozone, carbon monoxide, and a long list of hydrocarbons and their derivatives. The polycyclic hydrocarbons have been studied intensively as air pollutants mainly because some of them are suspected of being carcinogenic.

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*Read at the Regional Continuation Course on Chronic Respiratory Diseases in Children and Adolescents at the University of Minnesota, Minneapolis, September 17, 1968.

†Professor, School of Public Health, University of Minnesota, Minneapolis, Minnesota.

Toxicity

The toxic effect of a mixture of the different air contaminants is quite complicated; therefore it is not reasonable to consider each specific contaminant by itself. The synergistic actions of mixtures of different materials have not been evaluated in most cases. The problem is further complicated by the fact that each air pollutant may be present in varying amounts and the question of absorption of gases into liquids or adsorption on solid particles must be considered as well as the reaction of gases with other gases or particulate matter. The entire field of toxicology of air pollutants needs much further study.

Acute Exposure

Effects on human health of exposure to air contamination must be considered for either acute or severe exposures to relatively high concentrations of pollutants for a relatively short period of time or mild or chronic exposures to long periods of community air pollution. Throughout the world in the past three decades there have been several similar examples of acute exposures with definite effects on human health.

Weather and Temperature Inversions

In December 1930 an air pollution disaster occurred along the Meuse River Valley in Belgium.[1] A heavily industrialized area with numerous small communities was subjected to about one week of heavy weather including a continuous temperature inversion. A total of 63 persons died following this severe exposure and several thousand others were said to be ill. A serious episode occurred in October 1948 in Donora, Pennsylvania, with similar results.[2] A valley community, Donora, with a population of about 12,000, was subjected to four and a half days of stable weather conditions. There were twenty deaths, but more significantly it was found that about 50% of the citizens became ill from this exposure.

In November 1950 an industrial accident involving a flare used to control the release of hydrogen sulfide from an oil refinery operation caused the death of 22 persons in Poza Rica, Mexico.[3] At the time of the episode a temperature inversion was present over the valley community. In Poza Rica it was found that those who died included persons of different ages and states of health. In Belgium and Donora older persons with certain health impairments succumbed to the acute exposure.

The air pollution disaster with the greatest death total occurred in December 1952 in London, England, when about 4,000 deaths were attributed to a week-long smog period.[4] Again a temperature inversion along with stable weather conditions held the air pollutants close to the ground and the entire population was exposed. In this episode the normal death rates were greatly increased for older persons and also for infants under one year of age. Concentrations of sulfur dioxide in areas where the highest death rate was noted amounted to 0.6 part per million or less. This is not considered to be a hazardous exposure for humans and indicates that there must be a combined effect of different pollutants.

Community Exposure

The health effects from community exposure may result from a lifetime of living in an atmosphere with varying amounts of pollution. The Los Angeles smog is an oxidizing type of pollution primarily because ozone and other oxidizing substances are present in the air. The health effects from this type of pollution would undoubtedly be different from the reducing atmosphere with quantities of soot and sulfur dioxide as found in New York City, Chicago, Pittsburgh and most Midwest cities.

Most of the health effects are involved with the lungs and there is evidence to show a direct link between community air pollution and lung cancer, bronchitis, emphysema and asthma.

Of special interest to this group should be two recent studies on the health effects of children related to community pollution. Gol'dberg[6] reported on a study of Russian school children from eight to 12 years of age who were exposed periodically to emissions from a power plant located a few miles away from the school yard,[6] from which an average of 800 tons of fly ash and 350 tons of sulfur dioxide were dissipated daily throughout the atmosphere. It was found that 20% of the chest x-rays of these children resembled borderline silicosis. A later study was made on the same children after the contamination was removed and recovery was noted in some of the x-rays.

Another study[7] of[4] 3860 children in Britain for the first five years of their life and a reexamination of their lungs at ages six, 11, and 15, correlating the findings of the physical examinations with the smoke and sulfur dioxide indices, revealed that the upper respiratory infections were not related, but the lower respiratory infections were related, to community air pollution exposures.

Current Research

Studies on the pulmonary tissue reactions to ozone, oxides of nitrogen, sulfur dioxide, various hydrocarbons and synthetic smog, using nine different kinds of animals with varying concentrations and periods of exposure, have justified the following general conclusions:

1. Definite morphological and functional changes in lung tissue have been observed only when the concentrations are several times higher than those found in the atmosphere.
2. Tolerance to a given pollutant is developed by the animal exposed. To this end, animals exposed to low concentrations of ozone were later able to withstand supposedly lethal doses.
3. Exposure to certain gases increases animal susceptibility to bacterial infections.
4. The role of particulates along with gases in lung tissue reactions appears to be quite important.

Ozone

Sufficient evidence is available to show that acute exposures of ozone are highly toxic, yet reports of the morphological changes associated with ozone toxicity are relatively few. Microscopical investigations have been made using concentrations of ozone ranging from 0.2 to 50 ppm on mice, rats, hamsters, rabbits, and dogs. Methods of exposure varied from single doses for one to six hours, to multiple or continuous doses for up to 433 days. Morphological changes seen with the light microscope after a single dose are accumulation of edema fluid and migration of leucocytes into the alveolar space. Electron microscopy has revealed swelling and rupture of endothelial and epithelial cells and accumulation of cell debris in the alveoli. In prolonged studies chronic pneumonitis and contracted alveolar septa are seen.[8]

Nitrogen Dioxide

The effects of nitrogen dioxide on mammals are seen mostly in the respiratory tract. Experimental exposures as high as 400 ppm cause bronchopneumonia and death within minutes in laboratory animals. At 40-80 ppm severe ultrastructural alterations were seen in middle-aged mice exposed to NO_2 for about one hour. The same age animals exposed for 24 hours at 25 ppm showed slight damage to lung lining membranes. Very slight histopathology is evident with levels in the 0.5-5 ppm range continuously for 12 months or more.[8]

Other gaseous air pollutants have been studied even less for their histopathologic effects. Sulfur dioxide produces little or no morphologic change in lungs even with daily exposures of 25-50 ppm for a month. Severe ultrastructural damage to the lungs has been reported after 15-30 minutes of 0.5-1.0% carbon monoxide. Exposures of 700 ppm carbon monoxide for four hours have produced swelling of capillary lining cells and excess cell debris in capillaries of dog and mouse lungs. Tissue effects of pollutant mixtures are scarce and add more parameters to the already complicated literature.[8]

Conclusions

The disasters in Belgium, Donora, Mexico and London leave no doubt as to the effect on human health of acute exposures to air pollutants. However, there is considerable uncertainty about the effect of community exposures of large groups of people. The problem is a very complicated one and it will be difficult to develop conclusive proof on specific effects. Research on toxicology and pulmonary tissue reactions to different air pollutants is now under way.

Eventually it may be learned that human health effects from exposures to air pollutants could be quite pronounced. There is no doubt but that the concentrations of air pollutants have been steadily increasing and that more and more people are being exposed.

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Hamman-Rich Syndrome*

This syndrome is characterized by a generalized progressive pulmonary fibrosis of unknown etiology. The condition was first described in 1935 by Hamman and Rich who elaborated upon the subject in 1944. Approximately 41 cases have been reported. The syndrome is probably more frequently observed than the number of reported cases would indicate. It occurs most often between 40 and 50 years of age. Genetic and familial factors have not been emphasized, but there have been a few instances of occurrence in siblings.

The onset of symptoms is insidious. There is easy fatigability, weight loss, and intermittent or progressive dyspnea and cough. Pulmonary roentgenograms show a diffuse mottling. Eventually, clubbing of the fingers and toes and right-sided heart failure with cor pulmonale may supervene.

No specific bacteria have been isolated; the etiologic agent is considered most likely to be a virus. Diagnosis can best be established by pulmonary biopsy. Pathologic studies reveal an unusual inflammatory reaction with eosinophilic infiltration, absence of stainable bacteria, interstitial fibrosis, a diffuse collagenous hyperplasia in the interstitial peribronchial and perivascular areas, enlargement of the epithelial cells that line the alveoli, and necrosis of both bronchiolar and alveolar epithelium. Attention has been called to the similarity of the pulmonary pathology and a localized scleroderma of the lung. The syndrome may eventually be proved to be related to the collagen group of disorders.

The clinical course is characterized by irregular exacerbations. It may run a fulminating course of only a few weeks or continue for a few years. Sooner or later interruption of the alveolar oxygen exchange becomes progressive and respiratory and cardiac insufficiencies ensue. The therapeutic use of cortisone not infrequently affords temporary symptomatic relief, and there is roentgenographic evidence of some clearing of the pulmonary infiltration. It should be recognized, however, that the sudden discontinuance of cortisone therapy may result in a rapidly fatal outcome.

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*See Page 1366.

Cigarette Smoking and Chronic Respiratory Disease*

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MOST OF THE EPIDEMIOLOGIC and clinical studies of the relationship between cigarette smoking and chronic respiratory disease have focused on chronic bronchitis and chronic obstructive lung disease in the adult population. Cigarette smoking is less of a problem in chronic respiratory disease of children; however, it is reasonable to assume that the effects of cigarette smoke on the lungs will occur at whatever age the smoker may be. Hence all physicians who care for young people should take a positive stand in discouraging them from smoking.

For simplicity, the term "chronic respiratory disease" will be used to include chronic bronchitis, chronic obstructive lung disease, and emphysema; and wherever the word "smoking" is used, cigarette smoking is meant unless otherwise specified.

Clinical Experience

Clinical experience suggests a strong relationship between smoking and chronic respiratory disease in men, and several studies have documented a high prevalence of smokers among such patients.[1-3] Mitchell and associates[1] reported that only 5% of a group of patients with chronic respiratory disease were nonsmokers, compared to an estimated 20% of nonsmokers in a "control" population. Of 437 male patients with chronic respiratory disease who were 40 years old or more and were seen in our emphysema clinic, 5% had never smoked cigarettes, compared to 32% in an age-adjusted Mayo Clinic patient population from which most men with chronic respiratory disease had been excluded.

Clinical experience also suggests that patients with chronic respiratory disease who stop smoking fare better than those who continue. When patients do stop, we expect a significant decrease in cough and sputum and, less frequently, improvement in dyspnea. This impression is supported by reports that 63 to 73% of patients with chronic respiratory disease have a significant lessening of cough after stopping smoking.[1,4,5] And among those patients with chronic respiratory disease who stop smoking early enough for a decrease in cough and sputum, the mortality rate has been reported to be significantly less than among those who continued to smoke.[1,5] One study found no difference in mortality among smokers and ex-smokers except that those who stopped smoking after visiting a clinic fared better.[6]

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*Read at the Regional Continuation Course on Chronic Respiratory Diseases in Children and Adolescents at the University of Minnesota, Minneapolis, September 17, 1968.

†Mayo Clinic and Mayo Foundation: Section of Medicine.

There is very little information as to what happens to the pulmonary function of patients with chronic respiratory disease and a significant decrease in function when they stop smoking but have no other treatment. In young otherwise healthy smokers, abstinence from smoking for three weeks resulted in a significant improvement in peak flow, pulmonary diffusing capacity, and ratio of oxygen debt to increase in oxygen consumption after exercise. After six weeks without smoking, the functional residual capacity and airway resistance were decreased and the maximal voluntary ventilation was increased.[7] Among 17 patients with chronic bronchitis, however, Fletcher[8] found none whose ventilatory capacity improved significantly after they stopped smoking, though the rate of decline of ventilatory capacity was less steep in those who stopped smoking than in those who continued to smoke.

At the Mayo Clinic we have observed seven patients with chronic respiratory disease and significant decrease in function before and after stopping smoking without concomitant therapy. All reported a reduction in symptoms and four demonstrated an improvement in maximal breathing capacity and maximal midexpiratory flow. Therefore it appears that early in the course of this disease the changes in the airway, as measured by ventilatory tests, are reversible. When the process is advanced, the changes are much more fixed; even though symptoms decrease after smoking is discontinued, improvement in the results of ventilatory tests is variable and relatively slight.

Pathologic Changes

Mucous-gland hypertrophy, the hallmark of chronic bronchitis, has been well correlated with smoking though not with infection.[9,10] When sections of bronchial epithelium from smokers and nonsmokers were compared, those from smokers showed a greater number of goblet cells, more cellular atypism, increased thickness of the bronchial epithelium, greater infiltration of the bronchial epithelium with inflammatory cells, and shorter cilia.[11]

Emphysema

In a post-mortem study correlating the degree of emphysema with smoking, panlobular emphysema was found in a random distribution; but practically all lungs showing centrilobular emphysema came from smokers. The degree of emphysema was greater in older than in younger smokers and also greater in those with 40 or more pack years of smoking.[12] Auerbach and associates[13] found that the degree of rupture of alveolar septa was directly related to the amount of smoking and increased with age; but at all ages, men who had never smoked regularly had far less rupture than smokers. Associated with the disruption of septa were fibrosis, thickening of arteriolar walls, and pad-like attachments to alveolar septa. Ex-smokers who had stopped at least three years before death showed fewer changes than those who smoked to the time of their death. This type of change cannot be reversed by abstinence from smoking, but its progression can be halted.

It has been possible to produce alveolar disruption experimentally by exposing dogs to smoke in a smoking chamber[14] or through a tracheostomy so as to bypass the nose.[15] The lesions produced were considered to be analagous to those found in human emphysema.

Mechanisms Leading to Chronic Respiratory Disease

Increased Airway Resistance

By both direct[16-21] and indirect measurement[22] in smokers and nonsmokers, smoking one or two cigarettes has been shown to acutely increase airway resistance and decrease conductance.

Bronchitics and emphysematous subjects were found to have a greater increase in airway resistance than subjects without airway disease.[17,21] A decrease in compliance in normal as well as in emphysematous subjects after smoking one cigarette has been observed.[23] The apparent bronchoconstriction which has been attributed to irritation of the airway by smoke can be prevented by the administration of isoproterenol[19] or atropine.[20] These changes in airway resistance did not appear in measurements of vital capacity and maximal breathing capacity.[24]

In comparisons of chronic smokers with nonsmokers, the smokers have shown significant decreases in vital capacity,[25-30] expiratory flow rate as measured by any of several methods,[25-27,30-36] and airway conductance[37] and diffusing capacity.[7,28,38] It has also been found that smokers accumulate a greater oxygen debt during exercise than do nonsmokers.[27,39] Anderson and Ferris,[40] in an epidemiologic study which disclosed a significantly greater prevalence of chronic respiratory disease in smokers who had exceeded a threshold of 3,000 packages, found that the forced expiratory volume and the peak expiratory flowrate were decreased proportionately to the quantity smoked. They also detected effects of pipe and cigar smoking in the causation of chronic respiratory disease.

Reduced Bronchial Clearance

Some significant studies in experimental animals have disclosed other mechanisms whereby inhalation of smoke can foster the development of chronic respiratory disease. Bacteria are cleared rapidly from the respiratory tract of healthy mice, indicating that there is an effective clearance mechanism which maintains a sterile bronchial tree; but the inhalation of smoke reduced the clearance of bacteria by 50%.[41] Clearance of small particles that enter the alveoli is accomplished at least in part by phagocytosis.

It has been shown that the clearance of particulate matter is delayed significantly in the period immediately after exposure to tobacco smoke, though the mechanism recovers within 24 hours.[42] This anti-phagocytic action appears to reside in the gaseous or water-soluble component of the smoke, rather than in its particulate component.[43] Ciliary activity is responsible for clearing foreign material deposited anywhere in the tracheobronchial tree to the terminal bronchioles. Exposure to smoke of a variety of membranes containing cilia resulted in a sharp decrease in ciliary activity.[44-46] The ciliastatic effect of smoke also is in its gaseous phase, with hydrogen cyanide, acrolein, aldehydes, and certain acids being most ciliatoxic.

In recent years there has been speculation as to the possibility that disturbances in surfactant influence the disruption of alveoli. Several studies have shown that exposure to smoke decreases the surface-tension activity of material obtained from mammalian lung.[47-49] It has been proposed that this decrease in surface-tension activity or surfactant allows over-distention of large alveoli, thereby leading to rupture of these alveoli and to emphysema.

Summary

Clearly, there is much evidence to demonstrate a relationship between cigarette smoking and chronic respiratory disease; and some mechanisms whereby smoking may produce these changes have been described. Nonetheless, significant gaps in our knowledge remain. For example, not all people who smoke develop chronic respiratory disease in their lifetime, and a few people who have never smoked develop chronic respiratory disease. Smoke is recognized as an irritant to the bronchial tree, but how progression from simple bronchitis to obstructive airway disease and emphysema occurs is not understood. Possibly cigarette smoking is only one factor, albeit a major one, in the development of chronic respiratory disease; and other poorly understood factors such as individual susceptibility, heredity, infection, and exposure to other noxious agents help determine the rate, type, and degree of damage to the lung.

References may be found on page 1573.

The secret of being tiresome is in telling everything.—Voltaire

Flax Seed Poultice

(A Cataplasm)

Every now and again it is of interest for each of us to look into the past to see what was good in it and what was bad. This certainly applies to the practice of medicine in general and to the use of the poultice, or, as it was known, the cataplasm.

The poultice, which usually was made of a substance termed a counterirritant, has been used since antiquity. Its beneficial effect was felt to be produced by a dilatation of the blood vessels in response to warmth and moisture, thus increasing the blood flow and hastening the progression of the local inflammation to suppuration. Another and more nebulous explanation was that the substance diminished the cohesiveness of the tissue by insinuating itself between the cells, thus rendering the tissue more pliable and soft. Both of these actions tended to increase the swelling which was felt to be beneficial, since it seemed to lessen the tension and pain in the part affected.

Instructions for preparing the poultice were as follows: heat water in a basin until it boils; then sprinkle crushed flaxseed into the water, stirring vigorously till the proper consistency is attained. The substance should then be spread in uniform thickness onto a cloth and applied to the affected part.[1]

Common flax is an annual plant growing about two feet in height and probably originating in Asia or Egypt. Its fruit is a globular capsule about the size of a pea, containing ten seeds, which are oblong and somewhat pointed at one end, brown in color externally and yellow on the inside. The cuticle of the seed contains a peculiar gummy matter readily imparted to hot water, thus forming a viscid, mucilaginous fluid. Ground seeds become flaxseed meal; this has a mild gray color, is highly oleaginous and, when mixed with hot water, forms a soft adhesive mass, which makes an excellent emollient poultice.[2]

In the early 20th century the poultice fell into disrepute (at least in the teaching centers) and, in an official text,[3] was termed a filthy practice conducive to the multiplication of bacteria. Nonetheless, the practice of applying moist heat to an affected part continues to be an extremely important and often used treatment today for localized inflammatory conditions. The most exciting material used recently for local application is DMSO (dimethysulfoxide), an unusual solvent that is derived from a common waste product in paper manufacture. The list of beneficial effects produced by this peculiar substance is long,[4] and resembles in many respects those attributed to the old discarded flaxseed poultice.

Perhaps the poultice or cataplasm will have to be resurrected. Stranger things have happened.

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The Physiology of Immunity*

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It is appropriate to review the physiology of immunity and then see how the departure from this developmental process leads to certain respiratory problems directly resulting from immunologic deficiency.

The Recognizer Cell

We envision the antigen as being picked up by a cell which is not clearly defined morphologically and we can call this a "recognizer" cell of some sort (macrophage?). After this initial interaction the "recognizer" puts forth some kind of material that is called superantigen by many people and seems to bear some relation to RNA because if you treat such a material with RNAse it loses its potency. This material is picked up by another cell which we can denote as a processor cell. All of these steps seem to be necessary to produce the material that can be actually picked up by an effector cell and in the final analysis yield competent immunity. We have over the past few years divided immunity into those processes which seem to be more cellular in nature and dependent upon cells for their transmission and, on the other hand, those that are humoral, that is, carried in the fluid phase of the serum. The cells that are involved are the plasma cell for humoral immunity and the small lymphocyte for cellular immunity. There is certainly some relationship between the thymus and some effect of these central organs upon the recognition process (afferent limb) ; but again our knowledge on that is rather imperfect (Figure 1).

The Efferent Process

The immunological deficiency syndromes best studied involve disturbance of the efferent processes. As far as the afferent or "input" immune process is concerned we do not really know too much. There are two diseases that seem to be related to this process: *Aldrich syndrome* where there is a deficiency in recognizing antigens which have some sort of carbohydrate nature, and *fatal granulomatosis* associated with inadequate killing of intracellularly phagocytized organisms. The bulk of the immunologic deficiency syndromes that we have studied more extensively through the years have all been on the efferent side. We can diagrammatically envision how this comes about (Figure 2).

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†Department of Pediatrics, University of Minnesota.

First of all, there is some sort of primitive cell which is acted upon by the bursa or the thymus which bears a relationship to the lymphoid system similar to that of the pituitary and endocrine systems, being sort of master glands. A multipotential lymphoid stem cell which you might call an immunocyte traffics to the thymus, and from this interaction comes competent cellular immunity. In an alternative route the "immunocyte" is acted upon by an analogue of the bursa of Fabricius, an organ which is well characterized in the chicken and which probably has a counterpart in the intestinal tissue of mammals.

What can be seen in Figure 2 is that if there are processes acting at certain levels in the course of differentiation, the various known disease syndromes can be predicted. It is apparent that a defect of the "stem cell" or immunocyte results in an absence of both cellular and humoral immunity (Swiss type agammaglobulinemia or lymphopenic agammaglobulinemia). The milder forms, of course, would be where the process appears at a later point in this differentiation scheme, giving rise to primarily humoral deficiency or primarily cellular deficiencies.

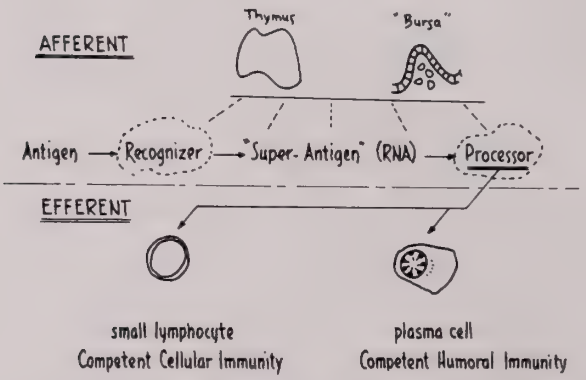

Fig. 1—The afferent (input) and efferent (output) limbs of immunity. The undefined regulatory influence of the thymus and "bursa" are indicated by dotted lines. The morphology of the cells involved in the afferent processing are as yet not wholly defined.

Cellular Immunity

Figure 3 shows a way of looking at the process of cellular immunity and how it reaches full expression. The cell that is of importance in carrying out cellular immunity is the small lymphocyte. It produces a compound called migration inhibition factor which is probably a chemotactic agent which attracts macrophages to the area where an interaction is taking place between antigen and lymphocyte. The macrophages amplify the system and produce the manifestations of the inflammatory response that we associate with this type of immunity. The role of complement in cellular immunity is not as well defined and seems to be more important on the humoral side, as we shall see. Now if one has intact cellular immunity, then he should be able to manifest all of the processes that we test by cutaneous delayed hypersensitivity. We feel that cellular immunity is important in protection against the processes of tuberculosis and monilial infections and in the prevention of generalized vaccinia; and it probably plays a role in giant-cell or Hecht's pneumonia.

Delayed hypersensitivity and cellular immunity are also of importance in the homograft rejection. Though all of these processes can help there are times when, in the process of the protection, the intensity of the inflammatory reaction is such as to cause damage to the host, so that, as an innocent bystander, the individual is harmed worse than the invading antigen. We feel that cellular immunity, when it gets out of hand, can give rise to a class of problems we know as the auto-immune disorders.

Immunoglobulins

As far as humoral immunity is concerned, the important mediators are immunoglobulins; we have at least five and I am sure more will be described in the future. The more important ones are IgG, IgA and IgM; IgG comprising about 85% of the normal immunoglobulins; IgA about 10% and IgM about 5%. The amounts of IgE and IgD are infinitesimal. As in the cellular system, something is needed to amplify the system because the initial reaction of the antibody with the antigen does not seem to do much. If complement is added to the system one can so magnify this reaction that it has profound biological implications. Thus with an intact humoral system you can carry out the processes of agglutination, phagocytosis, opsonization, chemotaxis and lysis, which provide full protection.

One of the interesting concepts of the role of immunoglobulins is that immunoglobulins may act in a protective way by covering cells and preventing anaphylactic reactions by occupying sites on effector cells so that complement cannot get on board. Furthermore, we feel that in certain instances immunoglobulins can coat cells and prevent the destructive action of complement. As in the cellular processes when the mechanism gets out of hand we have the destructive processes of the normal humoral immunity, e.g., the Arthus reaction, the antigen-antibody complex disease, post-streptococcal nephritis, lupus erythematosus and also auto-immune thyroiditis.

Amplification System

Figure 4 shows the amplification system of complement. There are nine components of the complement system and they seem to go on board a membrane surface after the antigen and the antibody combine. The complement continues in a sequence of one, four, two, three and so on to number nine. As these components are added, more biological processes become possible, such as chemotaxis, anaphylaxis, etc. Thus where there was originally an antigen-antibody reaction which was biologically impotent, now one can carry out the processes of immune adherence, chemotaxis, etc.

The persistence of more than one type of immunoglobulin over these many thousands of years of evolution indicates that there is a very definite survival advantage in having different kinds. If we look at the various processes that can be accomplished by humoral antibody and compare the various immunoglobulins one against the other we can see that there are certain specific advantages. For ex-

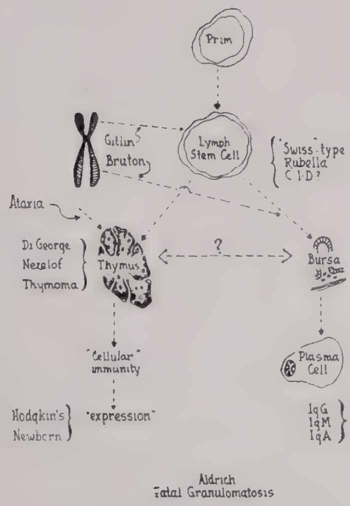
Prim
Gitlin
Bruton
Lymph Stem Cell
"Swiss-type
Rubella
C.I.D.?
Ataxia
Di George
Nezelof
Thymoma
Thymus
?
Bursa
"Cellular" immunity
Plasma Cell
Hodgkin's
Newborn
"expression"
IgG
IgM
IgA
Isolated "Dys-γ's"
Aldrich
Fatal Granulomatosis

Fig. 2—Production of immunological deficiency syndromes according to site of lesion along the developmental pathways. Aldrich syndrome and fatal granulomatosis probably do not involve these pathways. The pathways shown involve only the efferent limb.

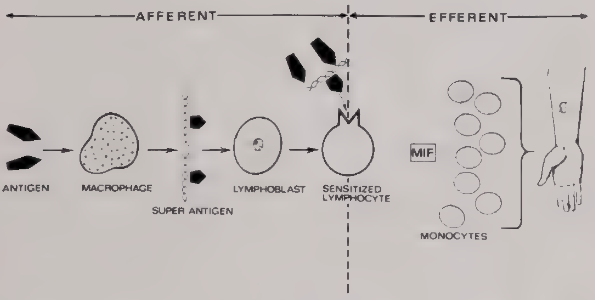
AFFERENT
EFFERENT
ANTIGEN
MACROPHAGE
SUPER ANTIGEN
LYMPHOBLAST
SENSITIZED LYMPHOCYTE
MIF
MONOCYTES
C

Fig. 3—Essential mechanisms involved in cellular immune reactivity as manifested by a positive skin test of the delayed hypersensitivity type. Similar mechanisms are brought into play in defense reactions of the cellular immune type. (From Childgren et al., Lancet I:1286, 1969. By permission of the publishers.)

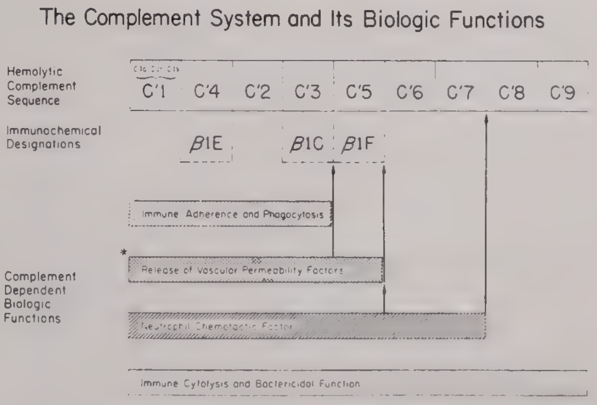
The Complement System and Its Biologic Functions
Hemolytic Complement Sequence
C'1
C'4
C'2
C'3
C'5
C'6
C'7
C'8
C'9
Immunochemical Designations
β1E
β1C
β1F
Immune Adherence and Phagocytosis
*
Release of Vascular Permeability Factors
Complement Dependent Biologic Functions
Neutrophil Chemotactic Factor
Immune Cytolysis and Bactericidal Function

Fig. 4—Biologic functions which amplify immune reactions as mediated by the complement system. (From Postgraduate Medicine, by permission of the publishers.)

ample, if you take agglutination and assign to IgG an arbitrary value of one, the IgM molecule is 750 times as effective as an agglutinator and more efficient in phagocytosis (about 2000 to one as Cf. IgG). We do not know the role of IgA and IgE in any of these processes. Complement fixation is two times as effective with IgM as compared to IgG. IgG, on the other hand, is the only protein that crosses the placenta and therefore provides passive neonatal immunity. Reagin activity has now been localized to IgE. That does not seem like a very beneficial process at the moment; I imagine that reaginic activity is probably an uncontrolled or destructive action, so that we shall therefore have to look further for the beneficial effects.

Blocking Antibodies

The concept of blocking antibody, of course, is very interesting to all physicians who treat chronic allergic syndrome, and work by Dr. Lichtenstein at Johns Hopkins has shown that upon sensitization by local injection you produce in the serum a lot of IgG antibody which has the ability to block the destructive IgE reagin. In the secretions, e.g., the saliva, the IgA is an important antibody which block, the IgE.

Localization to secretions stimulated by exterior influences is a characteristic quality of the IgA system. We feel that it may be of importance in providing local protection if, for example, you get invasion of the gastrointestinal or the respiratory tract. Rheumatoid factor activity is primarily the function of IgM. We think that the rheumatoid factor may be a form of protective type of activity and that the IgM may act to coat surface membranes preventing further antigen-antibody complex injury or blocking complement fixation.

Conclusion

In summary, we can conclude that IgM is probably important as a first line of defense; IgG is important for long-lasting immunity and the blocking of antibody, and IgA is important in local secretion.

The School of Salerno

What Meat To Eat

It followes now what part of every beast
Is good to eate: first know the Heart is ill,
It is both hard and heavy to digest.
The Tripe with no good iuyce our flesh doth fill:
The Lites are light, yet but in small request:
But outer parts are best in Physicks skill.
If any braines be good (which is a question)
Hens braine is best and lightest of digestion.

Regimen Sanitatis Salerni

The school has nothing good to say about heart and tripe; the lungs are without substance and rarely requested. The school advises that the skeletal muscle meat is most desirable. If brains are to be consumed, the authors roguishly add that hen's brains are in order.

The Nature of Disease

What disease is, is by no means a foregone conclusion, even if we eliminate all supernaturalistic explanations. Actually opinions about the nature of disease have greatly changed during the last 100 years and are still changing.*

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*Ackernecht, E. H., in Richard Macgraw: Ferment in Medicine, 1966.

One pancake for lunch and half a boiled egg for dinner makes a man at sixty able to do anything a college athlete can do.—William Osler

Hyaline Membrane Disease*

Danger of a Rational Approach to Therapy

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HYALINE MEMBRANE DISEASE has traditionally been thought of as having a 72-hour course with either death of the infant or recovery by that time. Although the disease is one of the major causes of death of the premature infant‡ it has been only in the last decade or so that sophisticated techniques of pulmonary physiology have been adapted to the premature infant. This information, compiled by a great number of investigators, has led to an increase in our understanding of the pathophysiology of this disease and to a therapeutic approach designed to overcome the physiologic derangements. Thus, by utilizing a rational approach to therapy we have been able to alter the course of this disease, but not without induced complications.

Incidence

The incidence of this disease is related to birth weight with the highest incidence, whether related to the number of births or to the number of deaths, occurring in the 1-1.5 kg group. In this weight range about 20% of liveborn infants are affected, and 45% of the deaths are from hyaline membrane disease. Considering all low birth-weight babies from 1-2.5 kg birth-weight, hyaline membrane disease affects approximately 8 to 10 percent of liveborn babies but accounts for about 40% of the deaths of these infants.

Pathology

Characteristically, the disease consists of severe atelectasis with dilated proximal bronchioles and alveolar ducts. It is in these dilated air-containing spaces that one sees the classical hyaline membrane and, therefore, the disease does not appear to be obstructive in nature.

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*Read at the Regional Continuation Course on Chronic Respiratory Diseases in Children and Adolescents at the University of Minnesota, Minneapolis, September 17, 1968.

†Associate Professor of Pediatrics and Physiology, University of Manitoba and Director, Respiratory Service, Children's Hospital, Winnipeg.

‡Now called the low birth weight infant.

Surfactant

One of the most significant advances in our understanding of this disease came in 1959 when Avery and Mead[1] reported that in infants dying with hyaline membrane disease the surface tension of the saline extracts of lung was abnormally high. The normal lung contains a surfactant which acts as an anti-atelectasis factor.

The transmural pressure or collapsing pressure of air spaces or alveoli connected in parallel is dictated by the LaPlace relationship which states that the collapsing pressure is proportional to the surface tension and inversely related to the radius of curvature. Thus, in alveoli of dissimilar size the collapsing pressure is highest in the smaller alveolus, which then tends to empty its air into the larger alveolus when the surface tension of the two alveoli is the same. However, the lung normally has an alveolar lining layer of surfactant which has the ability to lower its surface tension to very low values when the radius decreases. Thus the collapsing pressure of two alveoli of dissimilar sizes can be identical and there is no longer any tendency for small alveoli to empty into large alveoli. The term anti-atelectasis factor, therefore, seems appropriate when describing lung surfactant.

The pulmonary surfactant is presumably a lipoprotein complex, and the lipid portion of this complex is a lecithin, that is, a phosphatidylcholine which contains saturated fatty acids at the alpha and beta positions. Analysis of lungs of infants dying with hyaline membrane disease has revealed a decrease in the amount of disaturated lecithin. The lungs of infants who have died following recovery from hyaline membrane disease, and infants dying of non-pulmonary disease have higher concentrations of desaturated lecithin and very low surface tensions.

Pressure-Volume Studies

In-vitro studies of the lungs of infants dying with hyaline membrane disease have increased our understanding of the physiologic derangement in this disease. When these lungs are fully inflated to 35 cm of water pressure and the pressure decreased in 5 cm of water pressure decrements, the lungs of such infants contain less volume at each transpulmonary pressure when compared to lungs of newborn and stillborn infants without hyaline membrane disease. Furthermore, at zero transpulmonary pressure the lungs of babies with hyaline membrane disease cannot contain any air, but go on to complete collapse, while those of stillborn and newborn infants can still contain air following inflation even at zero transpulmonary pressure. This tendency to collapse, or atelectasis, is the fundamental problem in the disease.

Etiology

Over the years there have been numerous theories of the etiology of hyaline membrane disease, and to some extent our treatment of this disorder has been based on the theory of pathogenesis to which we happen to subscribe.

Aspiration of Gastric Content

One of the earliest theories was that of aspiration of gastric contents, but there is little evidence for this at the present time. However, the custom of emptying the stomach of premature babies at delivery still persists in many delivery rooms.

Asphyxia

There is no question that infants with hyaline membrane disease have lower Apgar scores at birth, suggesting that asphyxia may play a role. The increased incidence of the disease in the second of twins also supports asphyxia as a primary insult.

Cardiac Failure

There is little evidence on the basis of catheterization data that these babies have cardiac failure; however, there are some who feel digitalis is indicated.

Decreased Blood Volume

The decrease in mortality from hyaline membrane disease when the baby has had a large placental transfusion suggests that decreased blood volume may play a role.

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*See Test Your Word Score page 1401.

Deficient Fibrinolytic Enzyme

There are some studies which indicate deficient fibrinolytic enzymes in the lungs of babies dying with hyaline membrane disease. Whether these are primary or secondary to the disease is unknown, but there are nurseries where fibrinolysins are aerosolized to the lungs as part of the therapy, and the preliminary results are encouraging.

Altered Vagal Tone

Since vagotomy in animals results in pulmonary edema and hyaline membranes, and since severely ill babies with hyaline membrane disease have abnormally high constant heart rates, it has been suggested that the disease is associated with disturbed autonomic regulation.

Current Theories

The two leading theories at the present are that there is a primary deficiency of surfactant on the basis of prematurity alone, or that there is a primary defect in the pulmonary circulation, so-called pulmonary hypoperfusion or ischemia which secondarily alters surfactant. However, attempts at increasing the pulmonary circulation using acetylcholine have not improved the mortality rate from this disease.

Therapy

Energy Metabolism

The infants are kept warm, in a neutral thermal environment (anterior abdominal skin temperature of 36.5°C) which is associated with a minimal oxygen requirement. Oxygen is supplied in sufficient concentration to keep the arterial PO_2 within relatively normal values. The babies are given fluids and glucose for energy metabolism, and intravenous bicarbonate is used to correct metabolic acidosis.

Artificial Ventilation

In the presence of severe respiratory failure artificial ventilation is used to combat carbon dioxide retention and respiratory acidosis. The usual mode of artificial ventilation has been the use of endotracheal intubation and positive pressure respirators. However, recent reports by Northway[2] and co-workers from Stanford University have indicated that babies who receive prolonged artificial ventilation and high concentrations of oxygen are susceptible to the development of a condition termed bronchopulmonary dysplasia. We have seen this complication in our own nursery after about six days of endotracheal intubation and artificial ventilation.

Complications

Diffuse Interstitial Fibroplasia

This complication is characterized by the appearance of severe diffuse bilateral pulmonary infiltrations which appear after about six days of respirator therapy. The infiltrations may impart a "bubbly" appearance to the lung, not unlike that seen in the so-called Wilson-Mikity syndrome. The disease eventually progresses to a stage of marked hyperinflation of the lungs which can be recognized both clinically and roentgenographically.

The lungs of these babies show at post mortem a thickening of the alveolar septal walls with lymphocytic infiltration and multiple areas of fibroplasia and even collagen formation. We have not seen the bronchiolar epithelial hyperplasia described by Northway et al. and therefore have used the term diffuse interstitial fibroplasia to describe the roentgenographic and pathologic changes.

Over a 2½-year period at the Winnipeg Children's Hospital with a very highly selective and severely-ill population of infants we had 51 newborn infants who received artificial ventilation; 45 of the 51 were premature and 38 weighed less than 2 kg at birth.[3] Thirty-seven of the babies had an initial diagnosis of hyaline membrane disease and 14 of them required treatment because of aspiration pneumonia, tracheoesophageal fistula or a neonatal pneumonia.

Of those babies with hyaline membrane disease 27 were ventilated for less than six days and 18 of these died despite intensive therapy, reflecting the high mortality from this disease in the first few days of life. Of those who were ventilated for more than six days, two died and eight survived. Both of the babies who died had diffuse interstitial fibroplasia at autopsy. Four of the eight who lived had radiologic evidence of diffuse infiltrations on their chest films at one stage of their illness. Of the 14 who were ventilated for conditions other than hyaline membrane disease, diffuse interstitial fibroplasia again appeared only in five babies ventilated for more than six days. Thus, out of the total of 16 infants ventilated for more than six days, there were 11 examples of diffuse interstitial fibroplasia. We have had follow-up examinations of seven of the nine who survived, and surprisingly these diffuse infiltrations on the chest film have either disappeared or vastly improved, and these babies do not appear to have chronic respiratory difficulties.

Oxygen Therapy

Of those babies who were ventilated for more than six days, five had received high concentrations of oxygen (> 80%) for a period of less than 24 hours and despite this still developed diffuse interstitial fibroplasia. There were three who did not develop diffuse interstitial fibroplasia who also received high concentrations of oxygen for less than 24 hours. Of the nine receiving high concentrations of oxygen for more than 24 hours, six developed diffuse interstitial fibroplasia; yet there were three who did not develop this complication. Thus, it seems from our experience that there is no direct relationship between the duration of high concentration of oxygen therapy (> 80%) and the presence or absence of diffuse interstitial fibroplasia.

Endotracheal Tube

Some of the possibilities which have not been investigated thoroughly are that the endotracheal tube may in some way be related to the appearance of this disorder either by causing damage to the larger airways or by reducing effective ciliary activity, thereby resulting in abnormal accumulations of pulmonary secretions.

Constant Tidal Volume

There have been numerous studies in adult humans and animals which show that a constant tidal volume predisposes to areas of atelectasis and reduced lung compliance. That is, when one breathes at a constant tidal volume, the lungs tend to become atelectatic, and presumably this is why normal respiration is interspersed with frequent sighing and the occasional deep breath. That this may be a factor in this complication is a distinct possibility in view of recent preliminary reports by Doctor Stern of the Montreal Children's Hospital. In his nursery he does not use endotracheal intubation and positive pressure respirators for artificial ventilation. Instead, he uses a tank-type negative pressure respirator in which the baby, if he wants to, can cry to take a large breath. He has not seen this complication despite the use of very high concentrations of oxygen.

Other Complications

Other complications have arisen as a result of our current approach to therapy of hyaline membrane disease, such as pneumothorax, lobaratelectasis and pseudomonas infection secondary to the use of endotracheal tubes and respirators. Since the advent of the use of high concentrations of oxygen several cases of retrolental fibroplasia have appeared. To prevent retrolental fibroplasia we are now attempting to monitor the arterial oxygen tension in every infant by inserting a catheter into an umbilical artery. However, this procedure is not entirely benign since we have had one case of extensive thrombosis of the distal aorta and external iliac arteries.

Concluding Summary

Clinical experience has increased our understanding of the pathogenesis of hyaline membrane disease and suggests a therapeutic approach based on the correction of the physiologic abnormalities. Because of our experience with iatrogenic pulmonary disease it has become necessary to alter the approach to therapy. At the present time it is hoped that diffuse interstitial fibroplasia can be prevented by the use of endotracheal intubation and positive pressure ventilation for a maximum of six days. If artificial ventilation is needed after that, the babies will be transferred to a tank-type respirator. In addition, frequent measurement of arterial oxygen tension and much closer attention to frequent suctioning and pulmonary toilet seem to be important. It is too early to tell whether this regimen will make any difference.

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*References may be found on page 1575.

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Indication—Oral contraception.

Contraindications—Thrombophlebitis, thromboembolic disorders, cerebral apoplexy or a past history of these conditions, markedly impaired liver function, known or suspected carcinoma of the breast, known or suspected estrogen-dependent neoplasia, undiagnosed abnormal genital bleeding.

Warnings—Watch for the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, retinal thrombosis); if present or suspected discontinue the drug immediately.

British studies reported in April 1968[1,2] estimate there is a seven- to tenfold increase in mortality and morbidity due to thromboembolic diseases in women taking oral contraceptives. In these controlled retrospective studies, involving 36 reported deaths and 58 hospitalizations due to "idiopathic" thromboembolism, statistical evaluation indicated that the differences observed between users and non-users were highly significant. The conclusions reached in the studies are summarized in the table below:

Comparison of Mortality and Hospitalization Rates Due to Thromboembolic Disease in Users and Non-Users of Oral Contraceptives in Britain.

Category	Mortality Rates		Hospitalization Rates (Morbidity)
	Age 20-34	Age 35-44	Age 20-44
Users of Oral Contraceptives	1.5/100,000	3.9/100,000	47/100,000
Non-Users	0.2/100,000	0.5/100,000	5/100,000

No comparable studies are yet available in the United States. The British data, especially as they indicate the magnitude of the increased risk to the individual patient, cannot be applied directly to women in other countries in which the incidences of spontaneously occurring thromboembolic disease may differ.

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or sudden onset of proptosis, diplopia or migraine. Withdraw medication if papilledema or retinal vascular lesions are found.

Since the safety of Ovulen in pregnancy has not been demonstrated, it is recommended that pregnancy be ruled out for any patient who has missed two consecutive periods before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule the possibility of pregnancy should be considered at the first missed period.

A small fraction of the hormone agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect on the nursing infant cannot be determined at this time.

Precautions—Pretreatment physical examination should include special reference to the breasts and pelvic organs, and a Papanicolaou smear.

Endocrine and possibly liver function tests may be affected by Ovulen. Therefore, it is recommended that such tests if abnormal be repeated after the drug has been withdrawn for two months.

Pre-existing uterine fibromyomas may increase in size under the influence of progestogen-estrogen preparations.

Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.

In breakthrough bleeding, and all irregular vaginal bleeding, consider nonfunctional causes. Adequate diagnostic measures are indicated in undiagnosed vaginal bleeding.

Carefully observe patients with a history of psychic depression and discontinue the drug if severe depression recurs.

Any possible influence of prolonged Ovulen therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study.

A decrease in glucose tolerance has occurred in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be observed carefully while receiving Ovulen.

Because of the effects of estrogens on epiphyseal closure Ovulen should be used judiciously in young patients in whom bone growth is not complete.

The age of the patient constitutes no absolute limiting factor, although Ovulen therapy may mask the onset of the climacteric.

The pathologist should be informed of Ovulen therapy when relevant specimens are submitted.

Adverse Reactions—A statistically significant association has been shown between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: cerebrovascular accidents, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, breast changes (tenderness, enlargement, secretion), change in weight, changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post partum, cholestatic jaundice, migraine, allergic rash, rise in blood pressure in susceptible individuals, mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme and nodosum, hemorrhagic eruption, itching. The following laboratory results may be altered by oral contraceptives: hepatic function: increased sulfobromophthalein and other tests; coagulation tests: increase in prothrombin, Factors VII, VIII, IX and X; thyroid function: increase in PBI and butanol extractable protein bound iodine, and decrease in T^3 uptake values; metyrapone test; pregnanediol determination.

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References: 1. Inman, W. H. W., and Vessey, M. P.: Brit. Med. J. 2:193-199 (April 27) 1968. 2. Vessey, M. P., and Doll, R.: Brit. Med. J. 2:199-205 (April 27) 1968.

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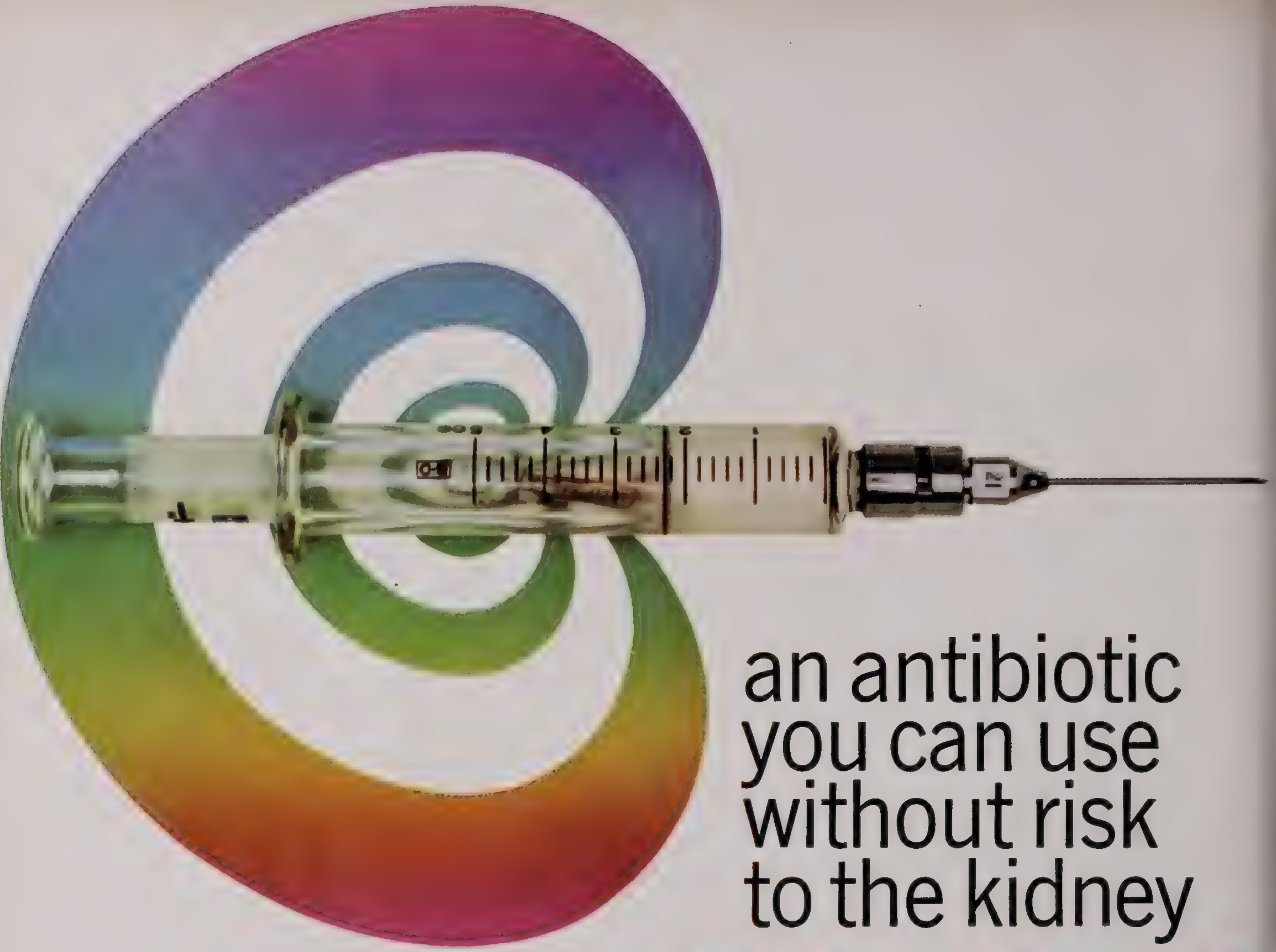

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Contraindications: A history of allergic reactions to penicillins or cephalosporins and infections due to penicillinase-producing organisms.

Precautions: Typical penicillin-allergic reactions may occur, especially in hypersensitive patients. Mycotic or bacterial superinfections may occur. Experience in newborn and premature infants is limited and caution should be used in treatment, with frequent organ function evaluations. Safety for use in pregnancy is not established. In gonorrheal therapy, serologic tests for syphilis should be performed initially and monthly for 4 months. Assess renal, hepatic and hematopoietic function intermittently during long-term therapy.

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Editorials

The National Cystic Fibrosis Research Foundation and Chronic Respiratory Disease in Children and Adolescents*

At a time of increasing complexity in science and society alike, there is a paradox at work. On the one hand we are forced into separateness and specialization; on the other, there are growing areas of shared interest, endeavor and knowledge. Certainly this is true in the field of diseases with which the present issue of Minnesota Medicine is concerned.

In 1955 the National Cystic Fibrosis Research Foundation was organized to combat this disorder. That year it awarded its first grant for research. Three years later, in response to increasing evidence of concern among parents, physicians and the general public, the National Institutes of Health also made grant funds available for research in cystic fibrosis. Both organizations have subsequently continued and greatly expanded this support.

Meanwhile, in 1961, a start was made by the National Cystic Fibrosis Research Foundation to establish a network of Cystic Fibrosis Care, Research and Teaching Centers. With the medical schools' cooperation, these were set up in teaching hospitals. Forty centers and 58 cystic fibrosis clinics eventually were in operation. Because many patients referred to them turned out not to have cystic fibrosis but to be suffering from other pulmonary or gastrointestinal disorders, a pattern of service was set that still persists: the majority cared for in these facilities are non-cystic fibrosis patients and are being treated for asthma, bronchiectasis, chronic bronchitis, and other chronic pulmonary diseases. It has followed quite naturally that the Center-clinic staffs have become recognized in their communities as outstandingly qualified to deal both with cystic fibrosis and with these various related conditions.

Something analogous has taken place in research. In the fall of 1965 the National Cystic Fibrosis Research Foundation inaugurated a series of basic research conferences, each one devoted to a subject such as molecular genetics, the autonomic nervous system or the nature of the secretory defect and its location in the sweat gland of the person with cystic fibrosis. Early in 1968 a Symposium on Cystic Fibrosis and Related Human and Animal Diseases was co-sponsored by the Foundation, the National Institute of Arthritis and Metabolic Diseases and the National Center for Chronic Disease Control of the Bureau of Disease Prevention and Environmental Control, U.S. Public Health Service. Over the course of these and other scientific meetings, there has been a shift from the exclusive concentration on cystic fi-

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*Read at the Regional Continuation Course on Chronic Respiratory Diseases in Children and Adolescents at the University of Minnesota, Minneapolis, September 17, 1968.

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brosis to consideration of molecular diseases in general, and from investigators not previously associated with cystic fibrosis have come valuable insights and suggestions.

When Washington decided last year to create pediatric pulmonary centers, grants went to groups that had already had experience conducting Cystic Fibrosis Centers.

The Regional Continuation Training Course in Cystic Fibrosis and Chronic Lung Disease held September 17-19 at the University of Minnesota Medical School was one of a series sponsored jointly by the National Cystic Fibrosis Research Foundation and the Bureau of Health Manpower Educational Services. The courses are designed to disseminate the latest knowledge about cystic fibrosis and chronic lung disease among members of the medical profession and to acquaint them with resources for further information and training.

As we get deeper into our age of specialization—sometimes thought of as an age of alienation—it is possible to point to greater interrelatedness among physicians, scientists, the government and voluntary health agencies. I firmly believe that, beyond present benefit, this is a portent of things to come.

John F. Herndon, Ph.D.*
New York, New York

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*Vice-President for Medical Affairs, National Cystic Fibrosis Research Foundation, New York, New York.

The Chronic Respiratory Program in the Minnesota Crippled Children Services*

In 1961 many physicians requested financial relief for parents whose children needed many expensive drugs for their chronic respiratory disease. Consequently Crippled Children Services began to provide drugs for these children as well as the diagnostic and treatment services when their parents were unable to provide the care.

The drugs and pulmonary exercises gave bright hope for many children. Parents and physicians were eager to avail themselves of these new advances in treatment.

Administration

All Minnesota children under 21 years of age are eligible for diagnostic services without charge to their parents. These services are available at the general itinerant field clinics, pediatricians and the two medical centers.

Applications for treatment can be obtained from the County Welfare Departments. A social worker will assist the parents in completing the application form. A medical report is needed to complete the application.

Eligibility of the child for treatment is determined by the Commissioner of the Department of Welfare. Consideration is given for other health needs in the family. The parents are notified by the Crippled Children Services as to whether or not the child is accepted for care. It is necessary that the application be approved and the necessary authorizations be issued prior to service.

Emergency service can be arranged for a patient by telephone or wiring the Crippled Children Services.

Physician services, including laboratory and x-ray services, hospital care, and a wide range of drugs are provided. Prescriptions are sent to the Crippled Children Services office, where they are filled by a pharmacist; then the drugs are mailed or sent by bus to the parents. Aerosol equipment is usually purchased by the parents or the County Welfare Department.

Findings

From the beginning of the program for chronic respiratory disease in May, 1961, to July 1, 1968, 85 children in 69 families have received care. Sixteen (23 per cent) of these families have had two, three or four children with chronic respiratory disease. Females (52 per cent) have predominated.

When the size of the family was plotted against the family's gross income group, eight families (12 per cent) were eligible for the medical assistance program.

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*Read at the Regional Continuation Course on Chronic Respiratory Diseases in Children and Adolescents at the University of Minnesota, Minneapolis, September 17, 1968.

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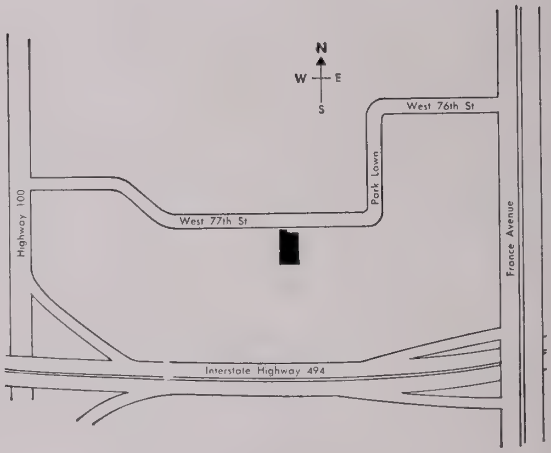
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TABLE

The Number of Children Served and the Cost of Care for Children with Chronic Respiratory Disease

Fiscal Year	Number of Children	Cost			
		Drugs	Physician	Hospital	Total
1960-61		$ 2,182.76			$ 2,182.76
1961-62	17	2,965.80	$605.00		3,570.80
1962-63	19	5,679.78	300.50	$ 1,215.50	7,195.78
1963-64	31	7,011.90	367.25	2,591.37	9,976.52
1964-65	37	8,709.88	420.25	2,612.29	11,742.42
1965-66	50	15,351.06	677.05	11,815.07	28,786.18
1966-67	58	19,393.94	630.30	8,412.62	28,349.11
1967-68		18,526.40	597.30	14,015.79	33,139.49

As these children have been followed, two of them have moved out of the state, and three were discharged at 21 years of age. Fifteen children from the 12 families have been removed from the treatment program because of the parents' ability to pay for their care.

Nine children (three males, six females in eight families) have died. The age range at death was from four months to 18 years; the average age was 8.4 years.

The number of children (Table) served in each fiscal year has increased from 17 to 58 from 1961-62 to 1966-67. The cost of the program has gradually increased from $2,182 in 1960-61 to $30,454 in 1967-68. Insurance payments are utilized but are usually not available for office visits or drugs. The cost of drugs (64 per cent) has been the most expensive part of these children's care. The average cost of care per child in 1966-67 was $488.

Conclusion

From the beginning of Minnesota's chronic respiratory program from May, 1961, to July 1, 1968, 85 children from 69 families have received diagnostic and treatment services when their parents were unable to provide the necessary care. Nine children (11 per cent) have died in this interval at the average age of 8.4 years. Twenty-three per cent of the families have two or more children with chronic respiratory disease and 88 per cent of the families are in the middle class.

There has been a gradual increase in the number of children provided for under the program and a corresponding increase in the cost of the program. The cost of drugs was 64 per cent of the total cost. The average cost of care for each child in 1966-67 was $488.

Mildred A. Norval, M.D.*
St. Paul, Minnesota

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*Director, Crippled Children's Service, Minnesota Department of Public Welfare, St. Paul, Minnesota.

Public Health Nursing Care of Chronically Ill Children*

IN THE VERY NATURE of chronic illness in any age group lies the implication for a long period of care and management, with the home as a primary focus. Those in the home who bear responsibility for long-term care of any ill person need assistance with care, instruction in giving care themselves, understanding of the illness and of medical orders, and support in persevering in the face of physical, emotional and financial burdens. A whole new element is introduced which must somehow be absorbed if family life is to be continued with any normalcy. When the patient is a child, these needs are multiplied in intensity for the family and especially for the mother who is usually the person responsible for care. When the child's illness involves the respiratory system, difficulties in breathing are particularly frightening and distressing.

Regardless of social and economic status, most of us in our society find it difficult to accept a chronic illness, particularly one with a

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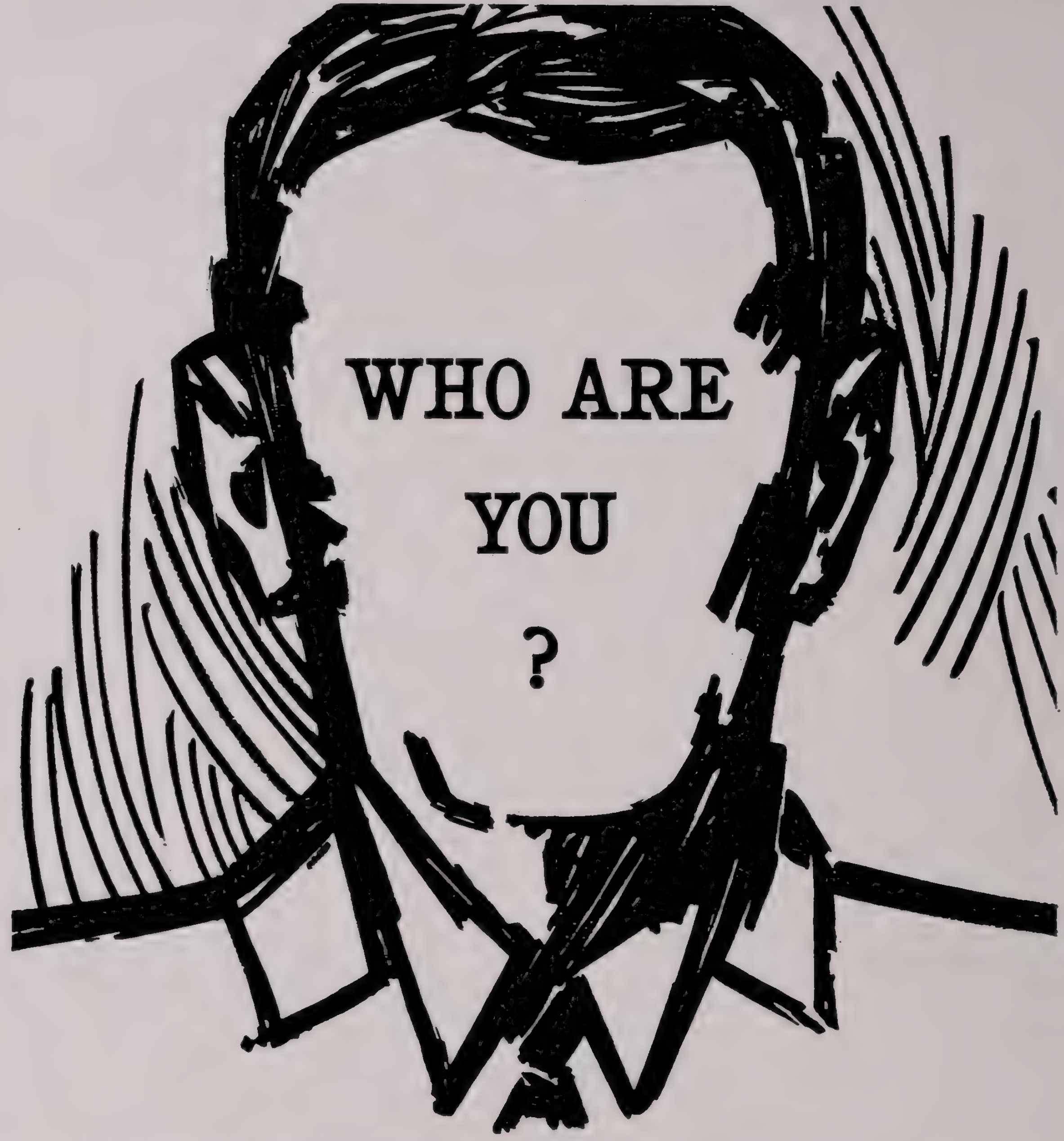
*Read at the Regional Continuation Course on Chronic Respiratory Diseases in Children and Adolescents at the University of Minnesota, Minneapolis, September 17, 1968.



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poor prognosis, at a time in the life of the individual that we believe should be a beginning, or at least a period without adult pain and worries. Such feelings are, of course, intensified for parents, especially if the illness has some genetic factor. Yet, in the face of such responsibilities and worries, a mother must somehow try to go about the business of beginning care if the illness is newly identified or resuming care if hospitalization has intervened in a long illness. The diagnosis of a child's chronic illness is usually a time of crisis, as is hospitalization or a crisis involving other family members. Death, of course, is the supreme crisis to be faced. If we are present in the home during or shortly after a crisis to help as needed, we may be able with relatively little effort to make a difference in the way a family adjusts initially; and the likelihood of our being more helpful in the long pull of chronic illness is greater, especially if subsequent crises are faced. Public health nurses can be helpful at such times; but their services are not and should not be limited to these.

We have the advantage of being able to go into the home, to work along with the mother in giving physical care if needed, in devising ways to give medications and to be sure these are understood, in setting up and using special equipment, and in planning for special diets. Above all we can visit often enough and long enough to give attention to the mother and her concerns and to consider with her the implications for the family. Even the most adequate mother who is busy with the care of a family as well as the care of a chronically ill child experiences a sense of isolation, and at times discouragement, as weeks and months—even years—provide no let-up in her responsibilities. The nurse can be supportive to her in many ways, depending on her needs and those of the child. She can give her some relief from actual physical care either by visiting herself or in some instances by teaching a practical nurse or home health aide how to give the care. She can encourage the mother to persevere in the often difficult tasks of treatment. She can help parents to consider such areas as school activities and to work with teachers if modifications are indicated.

In all of this, she must work closely with the physician in order to keep abreast of the physician's plan of treatment and changes in the child's condition. She can serve as a frequent and objective observer and reporter of progress and changes because she has a unique opportunity to be present in the midst of ordinary activity, without other demands being made on her for the moment, and to participate as needed in whatever care is required. She is also accepted, by many patients at least, as someone like themselves, yet as a professional who can listen to the day-by-day progress and problems, as someone who is not too busy and who understands. This may be all that some families need. If services other than nursing are needed, the nurse can often help to identify such needs and encourage families to seek other kinds of help and to follow through. Also she will need to work closely with physicians and workers providing other services.

Community nursing services receive some public support, either from taxes or voluntary funds, which enable them to give service at cost and to adjust charges according to a family's ability to pay. Medical assistance programs are available to families whose income falls below a specified level. In Minneapolis special programs are available, funded by the Childrens Bureau, to assist with medical care for children not eligible for other funds and living in the designated project area.

In most large cities public health nursing services are available on request from a visiting nurse association or a city health department. In Minneapolis these two agencies are combined into one nursing service for the city. Service may be initiated by a telephone call; but we require confirmation of telephone orders in writing. However, service can begin as soon as we receive a request and any necessary medical orders by telephone. In addition to the nursing services discussed, a physical therapist is available as a consultant to assist the nurse in carrying out exercise and rehabilitation programs.

In Minnesota services are available in 77 counties, and requests may be made directly to the County Public Health Nursing Service. Some of these nursing services provide consultation by a physical therapist, and some also have home health aides to extend public health nursing services. In the 10 counties without

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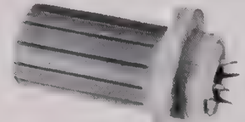

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such service, provision for care is varied and may be quite limited, but information can be obtained from the Nursing Section of the Minnesota Department of Health. There are eight district offices in which a nurse from the State Health Department serves as a consultant and knows the services available in her area. In other states, information about local nursing services can be obtained from the State Health Department.

Isabel T. McGarry, M.S.*
Minneapolis, Minnesota

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*Director, Home Health Services, Minneapolis Combined Nursing Service, Minneapolis, Minnesota.

Observations of a 28-Year-Old Man with Cystic Fibrosis*

THESE THOUGHTS of a 28-year-old man with cystic fibrosis are presented with the hope that they may help others to understand the problems of the young adult with that disease.

To parents I say, from the time your child is born with cystic fibrosis until the time he goes out into the world as an active and productive adult, you must keep a watchful eye and try to use the guidelines that govern the life of a normal child.

Try to instill in him the feeling that he is just as normal, within limitations, as most other children. He must be made to feel that he is part of humanity rather than a small singled-out specimen to be held in awe by others as well as himself!

Don't isolate him from the outside world. Teach the child, and especially the adolescent, to think for himself. As parents you have a real obligation to prepare each of your children for an active role in life. The obligation is even greater when you consider that your child is entering society with one black mark against him. *He has cystic fibrosis!* Early in life teach him how to solve his own problems; to run his own interference; to cope with the problems of living and to face the world on his own two feet. Don't be overprotective; love him but don't smother him.

As your child gets older and becomes an adolescent try to instill in him the feeling that he belongs to society and that he must some day in the not too distant future enter it on an active, productive level.

If he has always had to jump his own hurdles and to think for himself in his earlier years, he should be able to face the prospect of being a part of society as an active and productive individual, on par with a normal person.

In the 40s and 50s, when I was growing up, many children with cystic fibrosis died at an early age. Consequently, parents raised their "cystic children" in an over-protective manner and never gave much thought to the fact that the child would ever have to face the world. Presently, more and more cystic children are living well into their teens and adulthood; in fact, with the use of proper therapy, most cystics can have—within reason—a normal healthy life. With this idea in mind, the parent *must* gear the child and adolescent to that goal.

Give your child the proper therapy prescribed by your doctor! If the child is old enough to manage therapy himself, make sure he does so. I can't express too strongly the necessity of using a good therapeutic routine. Remember that if you are steadfast in using a good therapeutic program when the child is young, this same practice will manifest in the adolescent and young adult.

Put yourself in the position of the cystic: think to yourself "How would the world look to me if I felt ill all the time?" Then think "How much better the world looks if I feel well much of the time." I say that with the constant use of proper therapy the "cystic" *can* feel well much of the time.

When we have a sound mind and a healthy body, and in this case I mean a body that is therapeutically well cared for, we certainly can put our best foot forward and look ahead to a good life with a future . . . something we haven't had the opportunity to do in the past.

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*Read at the Regional Continuation Course on Chronic Respiratory Diseases in Children and Adolescents at the University of Minnesota, Minneapolis, September 17, 1968.

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To businessmen I say, an individual with cystic fibrosis has a chronic physical disability which can be managed with proper therapy, just as a diabetic is managed with insulin or a heart patient with digitalis.

We are coming into an age where medical progress has made it possible for these cystic children to grow to adulthood. In most cases these individuals are above average in intelligence and *can* be productive human beings. They *want* to be productive human beings: independent and self-supporting. But sometimes it is almost impossible, when everywhere they seek employment they are rejected because they cannot pass the physical or cannot be covered by company insurance. Whether or not they can fulfill the other job requirements is of no consequence. This is very discouraging! And after a person has been repeatedly rejected, he loses his determination and resigns himself to defeat. The result is depression and eventually the realization that life has no more future than death, since society will give him no chance to support himself.

Education of the public as to what cystic fibrosis really is, is a major concern to us now! In the next few years there will be many "cystics" looking for employment, and I hope that, with understanding, business and the public will be ready to receive them.

Parents have the responsibility of giving their children the guidance necessary to develop into independent, self-sufficient individuals who understand the importance of their therapy for the maintenance of physical health, thus enabling them to become ambitious, conscientious adults with the desire to work and lead productive lives as useful citizens.

Leo Altmeyer
Minneapolis, Minnesota

Letter to the Editor

As you probably know, the Massachusetts Medical Society is the oldest medical society with a continuous history in the country. At the present time, the Society is in the process of updating the statutes of 1781 that govern the organization. We began a series on the history of state medical societies, written by the editors of the various state medical journals in our January issue.

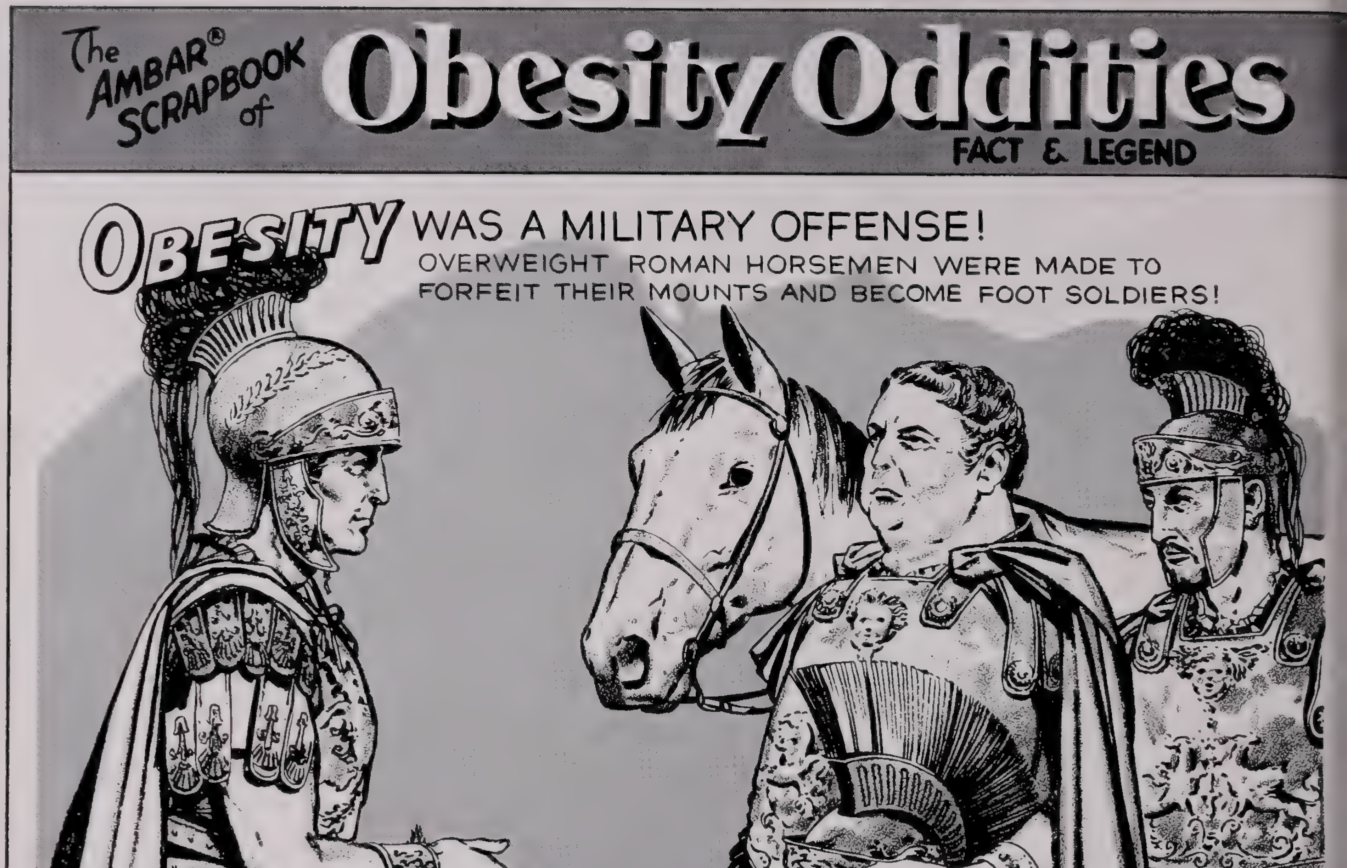
Can we prevail upon you to write an article on the Minnesota Medical Society and include germane information on MINNESOTA MEDICINE? If you find the suggestion intriguing enough and if your schedule allows it, may we have such an article? I look forward to hearing from you soon. Incidentally, I enjoyed the editorial on Purism and agree with the author's comments. I think your journal is absolutely super!

Carl Bearse, M.D.
Editor
MASSACHUSETTS PHYSICIAN

Government

Oh Lord, grant that we may not despise our rulers; and grant, oh Lord, that they may not act so we can't help it.—Lyman Beecher

The power of thought is the magic of the mind.—Lord Byron.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Letter to the Editor

For some time I have been planning to write to you to thank you for the complimentary copy of your fine journal which I receive monthly and which I presume you send to all AMA delegates. Now I am prompted to write both out of gratitude and out of curiosity.

First the gratitude: I enjoy and look forward to receiving your journal each month. After reading it I take it to the hospital for the library where it is read by another four hundred doctors and some sixty members of the House Staff. So you see we get considerable mileage out of your courtesy.

And now the curiosity: As a freshman medical student thirty odd years ago I spent one entire Sunday afternoon dreaming up a mnemonic for the branches of the external carotid artery. I finally came up with "All shyster lawyers enjoy sharing other people's surplus income." This has stood me in good stead for many years and I can still name the branches of the external carotid for whatever use that may be. I was intrigued by your note on Page 901 of the June issue of the MINNESOTA MEDICINE in which you refer to two well-known old-timers, but the "As she lay extended Sir Oliver . . ." was a brand new one to me. Inasmuch as my curiosity has gotten the better of my reticence I wonder if you would mind completing the quote?

Robert E. Zellner, M.D.
Orlando, Florida

Test Your Word Score

Surfactant—*surface tension lowering agent* (page 1382).

Atopy—*some form of allergy* (page 1407).

Heterozygous—*possessing different alleles in regard to a given character* (page 1430).

Tachypnea—*rapid respiration* (page 1436).

Choanal artesia—*congenital failure of the nose to communicate with the pharynx* (page 1446).

Bronchospirometry—*determination of the vital capacity, oxygen intake, and carbon dioxide excretion of a single lung* (page 1455).

Sympathomimetic—*capable of stimulating the sympathetic nervous system* (page 1469.)

Ceroid—*an insoluble pigment found in the fibrous tissue of cirrhotic livers.* (page 1512).

Botryomycosis—*granulomatous-like disease* (page 1547).

President's Letter

Medical Students

The demonstration by nearly 200 young people, including residents, interns, medical students and other groups at the A.M.A. convention in New York City on July 13 is well known to all of you. I can tell you, categorically, that the dissident medical personnel were in the minority. The others included heterogeneous groups seemingly demanding attention without valid reasons.

Seventy bonafide medical students, attending the House of Delegates, were nonparticipants in that irresponsible demonstration. A number of them came of their own accord to the headquarter rooms of a number of the state delegations to state that they did not agree with the demonstration and that these protestors did not represent student thinking. However, these students and a significant number of others do have a sincere concern relating to the field of medicine ranging from medical school admission policies and school curriculum, to the delivery of medical services. These students have become activists in promoting change. They are organized into two principal groups: the Student American Medical Association and a new group named Student Health Organization. Both of these organizations are becoming politically powerful.

The Student Health Organization, composed of medical, dental and nursing students plus various para-medical personnel, requested to be heard before the House of Delegates of the Minnesota State Medical Association meeting in Minneapolis in May, 1969. The spokesman for Student Health Organization made it clear to our House of Delegates that they first wished to become known to the practicing physician as friends and to get better acquainted with members of organized medicine. Student Health Organization policy makers state that they have great concern with social change and feel that such change be brought about through direct political action and community involvement. Their concern is for all levels of society including the disadvantaged: migrant workers, Indians, Mexican Americans, Blacks, and others.

The Student Health Organization has been active in several projects including participation in the Pilot City Health Care Center in Minneapolis, curriculum revision with emphasis on lectures on medical, social, urban, drug and alcohol problems and other topics, and racial and ethnic minority admissions to the health professions by changes in attitude of admissions committees.

The Student American Medical Association also has strong attitudes regarding changes in medicine.

Acknowledging that many responsible medical students are intensely interested in being heard by organized medicine and that these students do have many constructive and new ideas, our House of Delegates set up a subcommittee named the Subcommittee on Residents, Interns, and Medical Students. This subcommittee is meeting with representatives of the student body to study the problems that today face residents, interns, and medical students.

I believe these groups indicate a healthy movement for medicine. These young men and women will be the doctors of tomorrow, as well as the members and leaders of organized medicine. Let us support their constructive and new worthwhile ideas to the fullest extent.

Delmar R. Gillespie, M.D.
President
Minnesota State Medical Association

Editor's Soliloquy

Meleagris Gallopavo, Homo Sapiens, and Pig

THE KINSHIP of man, lower mammalian and avian species was again brought home to your Editor when a colleague was obtaining a history from one of his patients: an agriculturist suffering from a bleeding ulcer and a large abdominal aneurysm, who informed us that neither disease was new to him.

Pigs, he told us, are very susceptible to bleeding peptic ulcers: the leaner the hog the greater the danger. That made us wonder! By demanding our breakfast bacon lean may we not be building up frustration in Porky, whose very nature inclines him to be fat?

What's more—hogs can even become "nervous wrecks," when they are loaded on the truck for the trip to the slaughterhouse. Probably not so much because they don't know where they are going, but because they are too crowded on the way; which reminds us that psychologists say that too much togetherness can be devastating to the nervous system. Fish, rats, monkeys, don't behave or function normally when too crowded for too long. They become irritable, pugnacious, and averse to eating, sleeping and mating. Perhaps that includes Porky who, some hog raisers aver, is not the stupid, gross farmyard animal we thought, but indeed quite a sensitive fellow.

Abdominal aneurysms, our agriculturist further informed us, are a common disorder of the domestic turkey and, although aortic rupture occurs as a sporadic, spontaneous, fatal hemorrhage with flock mortality as high as 20 percent, the etiology remains obscure. Is it possible that our epicurean demand for broad-breasted Thanksgiving birds may have something to do with aneurysm phenomenon? Have we likewise interfered too much with the turkey's natural build and body proportions in order to serve more succulent white breast at our dinner table? I'm a thigh man, myself!

Our veterinary colleagues[1] from the St. Paul Farm Campus of the University of Minnesota have rendered us valuable service in producing lean, though nervous pigs, and broad-breasted, though aneurysm-prone turkeys. Also much commendable effort is being expended by the veterinarians in studying hypertension, heredity and hormonal factors on the production of porcine neurosis and meleagrine aneurysms. But it is here that our human and veterinary medicine must part—at least for the present.

Our agriculturist calmly submitted himself to the surgeon for replacement of the aneurysm with a new plastic aorta and a vagotomy for the bleeding ulcer. The eugenics can wait.

Carl O. Rice, M.D.

Reference

1. Krista, L. M.; Waibel, P. E.; Shoffner, R. N.; Sautter, J. H.: Natural Dissecting Aneurysm (Aortic Rupture) and Blood Pressure in the Turkey. Nature, 214:5093, 1162, June 10, 1967.

OLD DOC HESS SAYS: In my day when a girl was in need of a psychiatrist, she went home to mother instead—C.D.R.

Laboratory Letter

Triglycerides, Too

Can you sift out with a single test those patients who are destined to have a coronary occlusion? You can't, of course, not with one test or a dozen. But from the work of recent investigators, this much is clear—a serum cholesterol and serum triglycerides too can give you a rough idea of whether a patient is coronary-prone.[2]

Why? Because hypertriglyceridemia, like hypercholesterolemia, seems to predispose to premature atherosclerosis. Yet high serum triglycerides aren't necessarily coupled with high serum cholesterols. Kuo, for example, studied 286 atherosclerotic patients, many of whom were young men with coronary artery disease. Only 8.4% had an isolated high cholesterol, while 9.8% had only high serum triglycerides, and 81.8% had elevations of both.[1] To compare our data with his, I have taken sera on which we measured both triglycerides and cholesterol, separated out those samples where either or both tests were up (here I used Kuo's upper limits of 250 mg/100 ml for cholesterol and 150 mg/100 ml for triglycerides), and compiled the resulting data into Table 1.

As you can see from the table, if you had applied Kuo's upper limits to judge our patients' lipid status and if you had ordered only a cholesterol, you would have missed 44.4% of patients with hyperlipemia. A word of caution, though, lest you leap to conclusions. Though Kuo's upper cut-off points may be desirable, I don't consider them normal. I believe you ought to take age and sex into account before you label patients as abnormal. In Table 2, I show our age and sex-adjusted normal ranges.

TABLE 1

Distribution of Cholesterol and Triglycerides in 252 Sera

T.G.	Chol.	Number of Sera	Percent
normal	high	51	20.2%
high	normal	112	44.4%
high	high	89	35.4%

TABLE 2

Age and Sex-Adjusted Normal Ranges for Cholesterol and Triglycerides

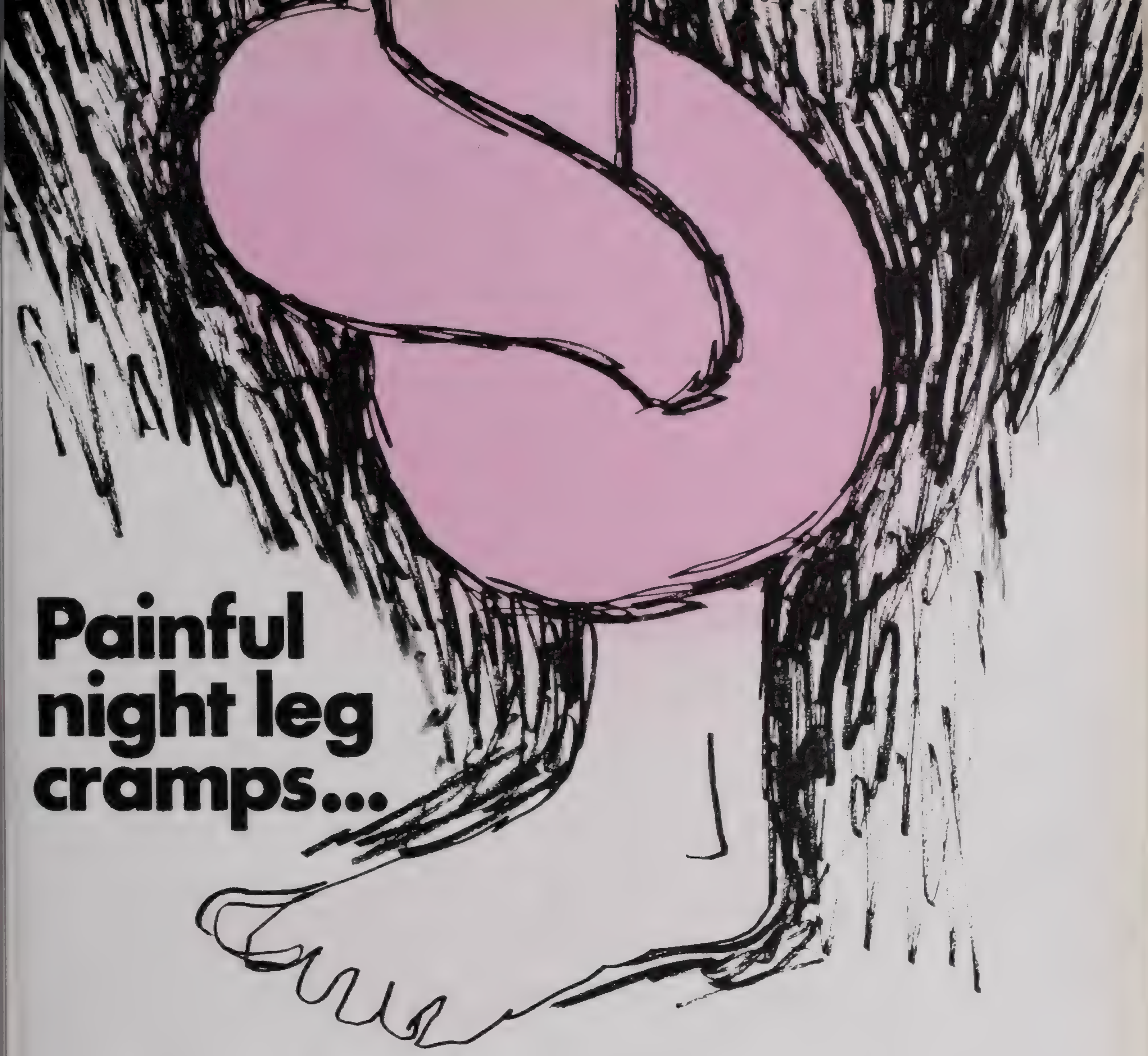
Age	Sex	T.G.	Chol.
20-29	M	10–140	110-215
	F		85-250
30-39	M	10–140	120-250
	F		125-265
40-49	M	10–150	135-305
-	F		135-265
50-59	M	10–160	150-310
	F		140-305
60-69	M	10–190	145-325
	F		150-325

Finally, a few practical points. First, triglycerides tend to be high in overweight patients with mild diabetes and coronary artery disease. Indeed, this cluster of findings is common in types II, III, and IV hyperlipoproteinemias. Second, by simply looking at a patient's plasma, you can sometimes surmise whether triglycerides ought to be measured. If the plasma is cloudy, the turbidity usually results from one of two things—a recent fatty meal or faulty lipid metabolism. If you allow the plasma to sit at 4C for 24 hours, exogenous triglycerides (chylomicrons) will form a creamy layer on top. Endogenous molecules will be distributed homogeneously.

Richard L. Reece, M.D.
Minneapolis, Minnesota

References

1. Kuo, T.: Hyperglyceridemia in Coronary Artery Disease and Its Management, JAMA 201:87, 1967.
2. Levy, R. I. and Glueck, C. J.: Hypertriglyceridemia, Diabetes Mellitus, and Coronary Artery Disease, Arch Intern Med, 123: 220-227, 1969.



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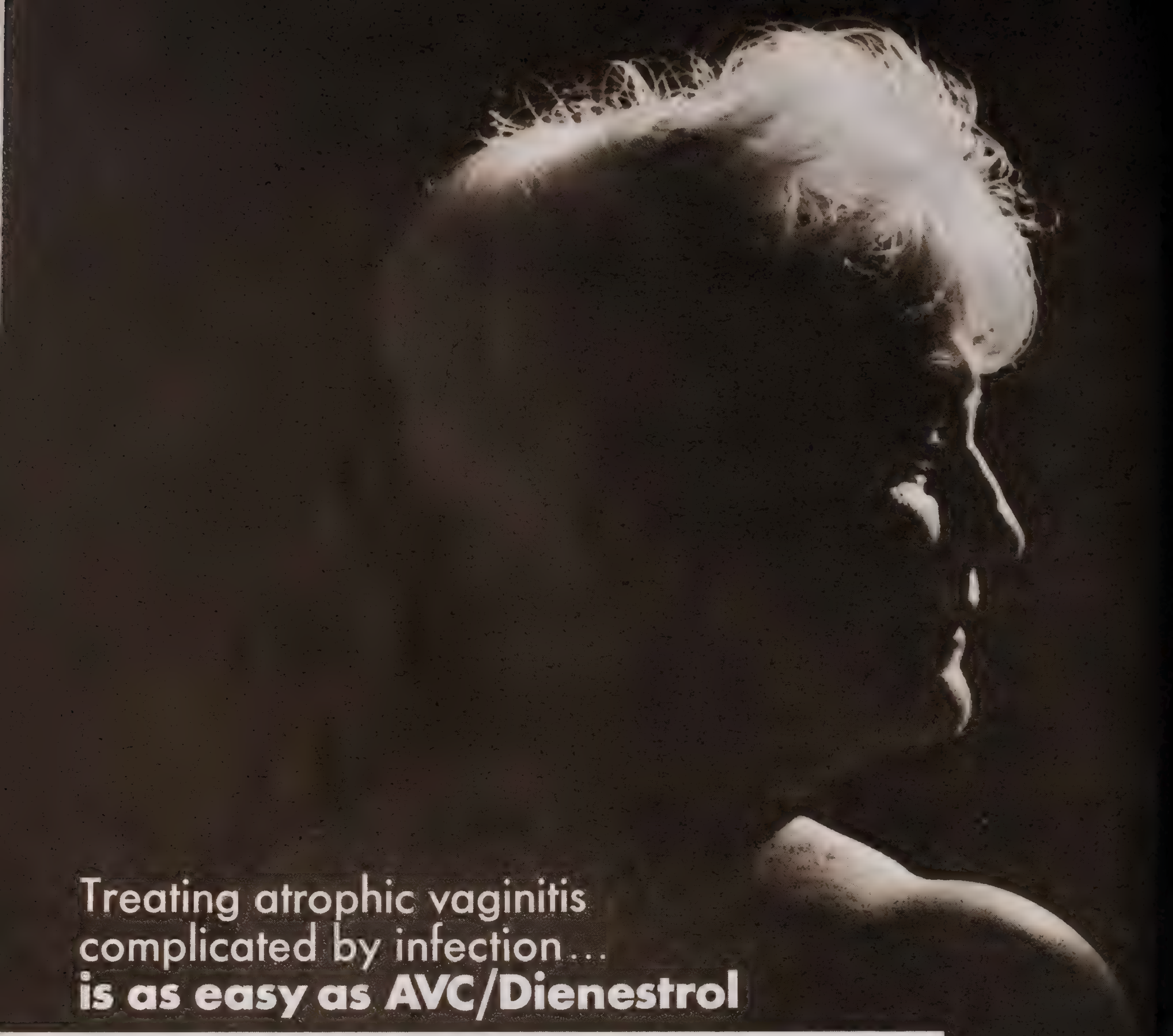
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References: (1) Salerno, L. J.; Ortiz, G., and Turkel, V.: Vaginitis: A Diagnostic and Therapeutic Approach, Scientific Exhibit, presented at the 115th Annual A.M.A. Convention, Chicago, Illinois, June 1966. (2) Nugent, F. B., and Myers, J. E.: Pennsylvania Med. 69:44, 1966.

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Etiology of Allergic Bronchial Asthma*

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Minneapolis, Minnesota

ASTHMA COMES from the Greek word meaning gasping or panting. It has thus been defined as that type of dyspnea produced by reversible, paroxysmal, generalized narrowing of the bronchiolar lumina.[1] Though most people feel they can easily recognize and diagnose correctly the condition commonly termed bronchial asthma, there is still much misunderstanding and confusion regarding the exact criteria necessary for the proper diagnosis.

There are two opposing groups with regard to what asthma is. The first believe that all that wheezes is not asthma. They insist that bronchial asthma is a disease initiated by an allergic mechanism which leads to the characteristic pathophysiology and symptoms. All other conditions which may produce identical pictures must not be termed bronchial asthma.[2]

At the other end of the spectrum is the group which states that all that wheezes is asthma. They prefer to indicate that the shortness of breath with cough, expectoration and wheezing caused by bronchospasm, edema and secretion, no matter what the underlying cause, is bronchial asthma.[3] In effect this group claims that asthma is a symptom or syndrome rather than a specific disease. Causes may be allergic, infectious, irritant or emotional, to mention a few.

Incidence of Bronchial Asthma

It has been estimated that about 0.5% of the general population will develop bronchial asthma. This is comparable to the statistics indicating that approximately 10% of the population will have atopy.‡ Bronchial asthma occurs all over the world and in all races. Eskimos and full-blooded Indians are said to have a low incidence. This could be due to a lack of asthma-consciousness among the investigators. There is little difference in the incidence of asthma between the sexes. Males predominate in the first decade of life and after the age of fifty; in the years between there may be a slight predominance of females. The disease may occur at any age. About one third of all cases of bronchial asthma on an allergic basis are said to develop during the first decade of life and probably over three fourths of them are seen before the age of 35. All evidence seems to indicate that social and economic status have no bearing on the incidence of asthma.[4,5]

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*Read at the Regional Continuation Course on Chronic Respiratory Diseases in Children and Adolescents at the University of Minnesota, Minneapolis, September 17, 1968.

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‡See Test Your Word Score page 1401.

Pathophysiology of Bronchial Asthma

The main symptoms in asthma are shortness of breath, wheezing, and cough. These result from the primary pathophysiologic processes: the bronchospasm, edema and tenacious secretions. Secondary consequences which may occur include dehydration, abnormal distribution of gas, hypoxia, hypercapnea, and increased work of breathing. Tertiary sequelae include right heart failure, infection, pneumothorax and atelectasis. The final clinical picture in allergic bronchial asthma is dependent upon the various pathophysiologic processes occurring and their consequences.[6]

Sequence of Events Leading To Bronchial Asthma

The sequence of events in allergic bronchial asthma leading to the above pathophysiologic changes has not been completely explained. It is thought that there must first exist the so-called "allergic state." This is a state in which these particular individuals are more likely to have symptoms of allergy than do others under exactly the same conditions. It is the soil in which allergy, in the usual sense, can flourish.

Sensitization

These people with the allergic state have the ability to become sensitized. What forces determine which patient becomes sensitive and which one does not are still unknown. Most likely, hereditary and environmental factors are of primary importance. A review of the statistical data on the familial incidence of allergic disease in asthmatics reveals that 40 to 70 per cent of them give a family history of allergy.[4] Several extensive attempts have been made to define the mode of inheritance of atopy, but the results have been conflicting.[4,7,8] There are several possible explanations for these discrepancies. First, there is no agreement with regard to the criteria of diagnosing atopy. Second, environmental factors may obscure the underlying genetic pattern. Finally, there may be multiple points at which genetic control could be exercised regarding susceptibility to the development of allergic bronchial asthma.[9] Examples of this might include the control of pollen allergens crossing the mucosal barrier of the respiratory tract, differences in antibody production, capacity of antibodies to enter into relationship to the antigen on the target organ, and responses to mediating substances. All of these could be under separate genetic control. Therefore, depending upon the frequency of the genes involved and the exposure to the allergen, a variety of genetic patterns may be encountered. The data on hand seem to indicate that there are genetic factors involved in the development of allergic bronchial asthma, although the exact mode is not clear.

Route of Entry

Environmental factors are of obvious importance regarding the initial exposure of the individual to sufficient allergic substances which produce sensitization. Allergens may enter the tissue by several different routes, including the respiratory system, gastrointestinal tract, skin, and by injection. The chief factors which influence the nature of the response in man include the antigen itself, the duration and intensity of exposure and the route by which the antigen enters. Farmers are exposed to pollen and animal dander in larger amounts than most urban dwellers. Workers in industries such as grain mills and resin factories are exposed to potent allergens normally not contacted by the general population.

The climate may also influence the allergic state. The antigens to which an individual is exposed will depend upon the vegetation which grows in his particular environment. In general, only those plants which are wind-pollinated and produce large amounts of buoyant, windborne pollens are important in the causation of allergic bronchial asthma. Plants such as flowers with strong odors are adapted to insect pollination and thus produce a relatively small amount of sticky heavy pollen;

hence they rarely cause bronchial asthma.[5]

Formation of antibodies

As we have already established, when an allergic person is re-exposed to an allergen which is not antigenic to others, he will respond with the production of specific antibodies. Reagin or skin-sensitizing antibodies are thought to be the main immunoglobulin involved. They are found in vascular and non-vascular fluid.[10] The relationship between circulating reagin and that found in the secretions is not clear. It may be that the antibodies occurring in secretions which are most likely involved in bronchial asthma are not derived from those produced in other parts of the body by plasma cells or lymphocytes and then go to the lung tissue. Rather, it is more likely that the antibodies are synthesized by plasma cells lying just below the epithelial cells of the respiratory tract.[11] These reaginic antibodies have been characterized by Ishizaka as associated with the IGE immunoglobulin.[12] Recent work by Johansson has confirmed these observations.[13,14]

Re-exposure Causing Antigen-Antibody Reaction

Although re-exposure to the specific antigen which the individual is sensitized to can come by any route, the respiratory tract is the most common in bronchial asthma. The location of the antigen-antibody reaction, though not definitely known, may be in the secretions, on the cells, or in the cells. Work by Ishizaka[11] and Tamaszi[12] has shown that in allergic persons ragweed antibodies are present in the external secretions.

Release of Intermediate Mediating Substances

The union of antigen with antibody is thought to produce the clinical picture of bronchial asthma either directly (through irritation or precipitation or changes in the cell enzyme) or indirectly (through the release of intermediate chemical products which in turn act on the lung tissue to cause bronchospasm, capillary dilation with edema and increased secretion). Although it has been demonstrated that the antigen-antibody complex *per se* has produced bronchospasm in non-sensitized tissues, it is felt by the majority that the actual manifestations of asthma are probably due to the action of the mediators at a secondary site, usually smooth muscle, glandular tissue and vascular tissue. The main mediating substances are thought to be histamine, slow-reacting substance, plasma kinin and serotonin. There is a sparsity in the literature of good data on the pharmacology of bronchial asthma. This is due in part to the marked differences between man and the lower animals with regard to the mediating substances.

Histamine

Histamine in man has been demonstrated to cause pruritis, skin erythema, a slight reduction in blood pressure, edema and, at times, generalized angioneurotic edema. In normal subjects, there is usually a complete absence of bronchospasm and severe hypotension using physiologic doses.[14] Nebulization with histamine in a non-atopic individual will cause evidence of bronchospasm; but the threshold is much higher than that for the patient with asthma.[15] Pre-treatment with antihistamines will prevent the formation of these histamine-caused symptoms. Histamine has been released *in vitro* from lung tissue of allergic individuals.[16] Antihistamines usually are not effective in combating the symptoms of allergic bronchial asthma. Histamines alone, therefore, account for only a limited number of the manifestations of bronchial asthma.

Slow Reacting Substance

A slow-reacting substance of unknown composition can cause a relatively slow contraction of smooth muscle. Antihistamines do not antagonize its action. It has been found in lung tissues of pollen-sensitive individuals. Human bronchiolar tissue, according to some investigators, is very responsive to it. Slow-reacting substance administered by aerosol has a bronchoconstricting action in asthmatic patients but has no such effect in normal subjects.[15]

Plasma Kinins

Plasma kinins, one of the many physiologically active polypeptides, have been thought to play an important role in bronchial asthma. They stimulate smooth muscle, cause vasodilation, increased capillary permeability, enhance the migration of leukocytes and stimulate pain fibers. Upon intravenous administration both kallidin I and II increase the resistance of the lungs of anesthetized guinea pigs to inflation. This bronchoconstrictor activity is antagonized by analgesics such as acetylsalicylic acid. Kallidin I by aerosol has no bronchoconstrictor effect in the guinea pig or in normal man. It does, however, initiate bronchoconstriction in the asthmatic patient. There is evidence that a physiologic role of kallikrein is the causation of vasodilation in glands, possibly leading to an increase in their secretions.[15]

Serotonin does not seem to be involved in the production of bronchial asthma in man.[15]

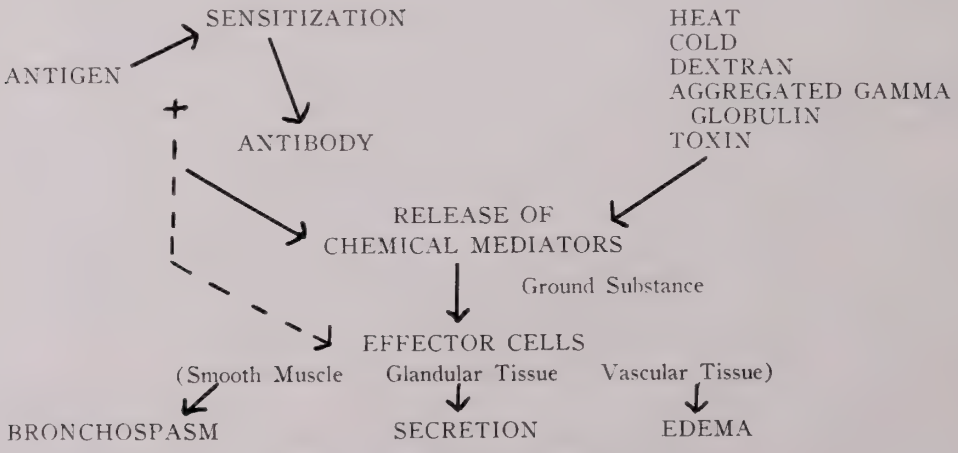
Effect of the Mediating Substances on the Tissue Structures

The mediating substances are thought to act on the tissue structure causing bronchospasm, edema of the mucosa and increased mucus. This in turn results in the clinical picture of bronchial asthma characterized by cough, shortness of breath, and wheezing. It is apparent that bronchial asthma is distinguished not only by the release of active substances but also by the exaggerated response of the bronchial tree to the chemical mediators. A number of reports have demonstrated that the respiratory tract in patients with asthma is overly sensitive to the actions of inhaled histamine, acetylcholine, slow-reacting substance and bradykinin.[16] Whether this heightened reactivity is due to some special property of the capillaries, mucous glands, smooth muscle or some other structure in the asthmatic lung or whether it is a cause or effect of bronchial asthma is unknown.

It is evident, however, that the mediators, once they are released or formed as a result of the antigen-antibody interaction, must travel through a finite intercellular space before reaching the effector cell. It has been suggested that the chemical characteristics of the intercellular space and the ground substance filling it are of primary importance in determining the activity of these chemicals on the effector cells.[16] Therefore the chemical pathology of asthma may involve the ground substance rather than a unique cell responsiveness.

Many have investigated the importance of the autonomic nervous system and the acetylcholine-cholinesterase system in bronchial asthma. It has been suggested that asthma may in part result from a functional imbalance between the alpha and beta receptors in the lung. Conflicting evidence seems to indicate that there is a decreased response with regard to the beta receptors.[17,18] Its importance in the clinical disease or whether it is a cause or effect of the condition has yet to be determined.

The importance of the acetylcholine-cholinesterase system has been stressed in the past. Many investigators feel that asthma is a disease of dysautonomia, suggesting that it represents



Figure—Etiology of Bronchial Asthma

a state of parasympathetic preponderance. Threshold doses of acetylcholine to produce bronchoconstriction were less in asthmatics than in normal subjects. Scattered reports of elevated levels of acetylcholine in patients with asthma have been published.[16]

Although the exact mechanism present in the production of the symptoms of bronchial asthma on an allergic basis is not known one can postulate essentially two main steps (Figure). First is the presence of an immunologic reaction characterized by sensitization with the production of antibodies followed by an antigen-antibody reaction. Next is the selectivity of the tissue which will react as the result of the antigen-antibody union. The finding that symptoms of bronchial asthma can occur without the presence of known antigens lends support to the concept that the antigen-antibody interaction activates a nonstable enzyme which in turn activates a mediating substance. Other factors have been shown to produce the same activation or release of mediating substances. Among these are heat and cold, low molecular compounds such as 48/80, and basic amines and high molecular substances such as dextran, endotoxin, aggregated gamma globulin and proteolytic enzymes.[15,19] Hence, one can say that all allergic asthma is due to a mediating substance being released. But not all mediating substances which are released can be traced to an antigen-antibody union.

Role of Allergens in the Causation of Allergic Bronchial Asthma

Allergens are the antigens which upon reintroduction cause pathological tissue reactivity or hypersensitivity. These allergens may attack different shock tissues and produce various clinical manifestations. Therefore the same allergen may cause asthma, hives, and a contact dermatitis in the same person.

It should be stressed that the allergens may be multiple and usually are. Also, allergens may be only part of the whole picture and may be greatly influenced by other factors. As pointed out, the allergic state is influenced by inherent predisposition, by exposure to allergic substances adequate to stimulate antibodies, and by yet unknown factors. This basic allergic state plus the exciting causes such as an extrinsic allergen like pollen and non-specific factors such as emotional state and fatigue are all factors which determine the type and degree of clinical picture.

Some persons are so highly sensitive to an allergen that even the smallest amount will produce symptoms. Others may tolerate small amounts but develop symptoms if exposed to larger quantities. Thus the allergic symptoms may be minimal, due to a balance state between the tolerance of the patient on the one hand, and the allergic and sensitized state and slight exposure. Tolerance may be outweighed by excessive exposure to the allergen; then clinical symptoms may result. Finally, despite slight exposure to the allergen, the allergic equilibrium may be disturbed by non-specific precipitating causes such as heat, cold, infection, psychic trauma and irritation.

Summary

Allergic bronchial asthma may be defined as a symptom complex in which there are paroxysms of reversible airway obstruction manifested as wheezing and dyspnea, triggered off by an allergen to which the person had been previously sensitized. As a result an immunologic reaction occurs with the release of mediating substances which in turn cause the primary pathophysiologic processes of edema, bronchospasm and secretions. There seems to be an increased sensitivity to the mediating substances in these patients. It should be stressed that in allergic patients with asthma, more than allergic factors need to be considered in its etiology. We must remember that allergic patients may have all other diseases that we are all heir to, and these may be the most important. Beyond that, non-specific factors may initiate, aggravate and complicate allergic bronchial asthma. Cold air, chemical irritation, high humidity, respiratory tract infection, and psychogenic factors are all examples of predisposing, complicating and precipitating factors. Their role in the causation of allergic bronchial asthma is often just as important as that of the specific allergen.

References may be found on page 1574.

In the physician or surgeon no quality takes rank with imperturbability.—Osler

Symbols in a life of
psychic tension

M.A.
class of '66

Ph.D.
thesis...in progress

G.I.
series and complete
examination normal
(persistent indigestion)

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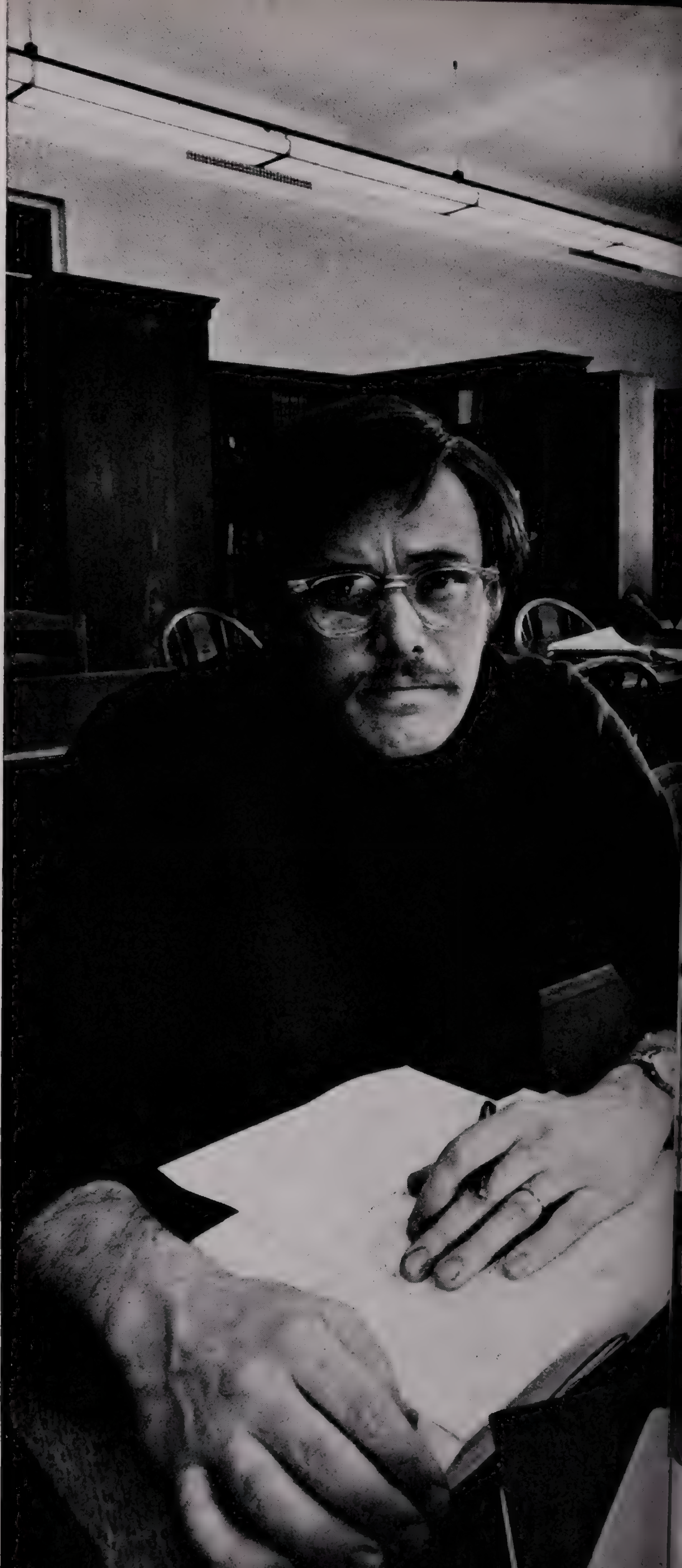

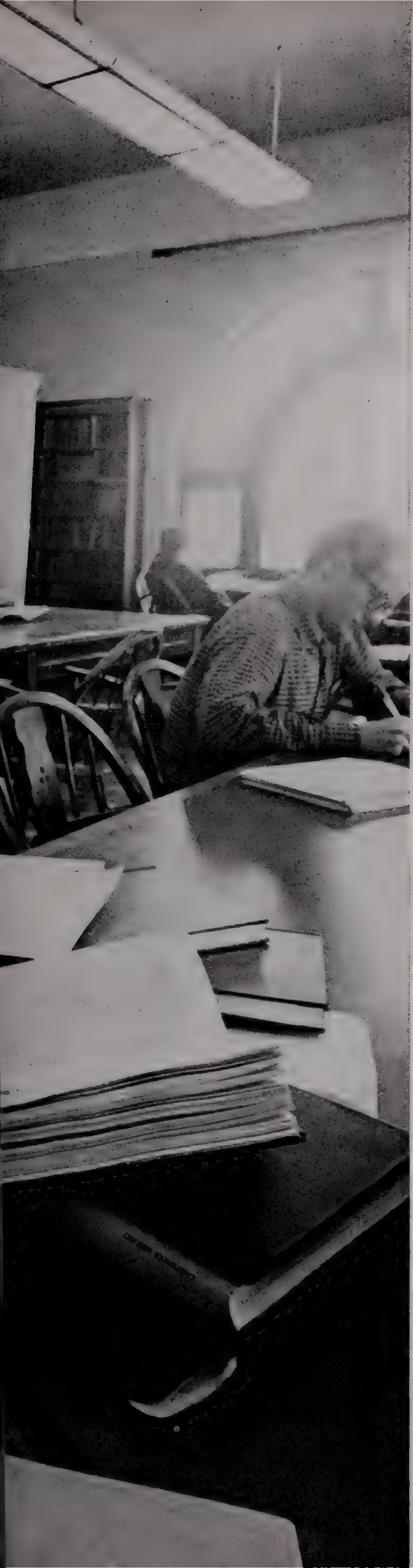

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Valium can help relieve psychic tension and resultant somatic symptoms, within the first day for some patients. Valium is also useful in psychic tension with associated depressive symptoms. And Valium can help relieve psychic tension-induced insomnia with an *h.s.* dose added to the *t.i.d.* schedule.

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Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms have occurred following abrupt discontinuance. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation, have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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to help relieve psychic tension
and its somatic symptoms

Federal Programs for Pulmonary Diseases

The purpose of this presentation is to assemble the concepts of "how to treat patients," "what kinds of patients you may have," and "what possible difficulties in diagnoses," and then relate these to the fact that you as a physician are a part of a community.

The Public Health Service in the last few years has developed what we consider a reasonable concept of looking at the patient and his community, and particularly the patient with a chronic illness. We call this a "Comprehensive Care Wheel."

We feel that the center of concern for any person in the health profession is the patient and his family, and that any health professional who sees a patient must think of *four areas.* He must look at the *physical,* the *psychological,* the *economic* and the *social* aspects of the problem. That, of course, doesn't mean that he treats all of them; but as a health professional he is required to consider these four areas no matter who the patient or the family may be. Then there must be some kind of *evaluation.* Possibly not by the health professional who made the original contact with the patient and his family; but there must be an evaluation and a *referral.* We feel that every community in the United States can divide its medical care services into three possible kinds of referrals. First, there is the classic in-patient referral that puts the person into the hospital or a medical treatment situation, nursing home, hospital, or a specialized hospital of some kind.

The second is an out-patient referral which requires an out-patient clinic that may be free standing. Also included in this concept is the private practitioner's office which is a kind of out-patient service, for when the patient comes, the diagnosis and treatment outline is made and he may then be asked to return unless he is placed in an in-patient treatment system.

Finally, there is the possibility of home care, and in this area we are just beginning to have services available in most communities. I don't know why it has taken us so long to get back to the old-fashioned way of taking care of people, i.e., keeping them in the home so that they can have around them the people that will give them the emotional support and help to recover from the shock of illness. Fortunately we are now developing services that can be dispensed from a central in-patient or out-patient building or taken into the home.

For instance, a community must provide *personnel* of some kind. (Most of us are provided by the community.) There must be *some funds and some facilities* from the community; otherwise there will be no medical services of any dimension. There must also be *research and training* provided by the community, and finally, some *coordination and administration,* or at least some plan therefor if this *care* wheel is to function in any community.

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New York, New York

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*Assistant Commissioner, Preventable and Chronic Disease Services, Department of Health, The City of New York, New York.

Derivatively Speaking

Embolus—from Greek *embolos* (a plug)

Congenital Cardiac Disease*

Causal Factor in Pediatric Pulmonary Disease

RUSSELL V. LUCAS, JR., M.D.†
Minneapolis, Minnesota

CHILDREN WITH CONGENITAL cardiac disease have frequent pulmonary complications which contribute a significant limiting factor in successful management of these infants. Approximately 50% of children born with congenital heart disease die within the first year of life.

Cardiac disease influences all components of the respiratory system through a variety of etiologic mechanisms as outlined in the Table.

Alterations in the Pulmonary Vascular Bed

Understanding of the effects of cardiac disease on the pulmonary vascular bed is enhanced by an appreciation of the normal maturation of the pulmonary vessels. During fetal life and at the moment of birth, pulmonary arteriolar resistance is equivalent to systemic arteriolar resistance as a consequence of thick-walled, narrow-lumened pulmonary arterioles[1,2,3] (Figure 1, *left*). Pulmonary vascular resistance drops significantly in the

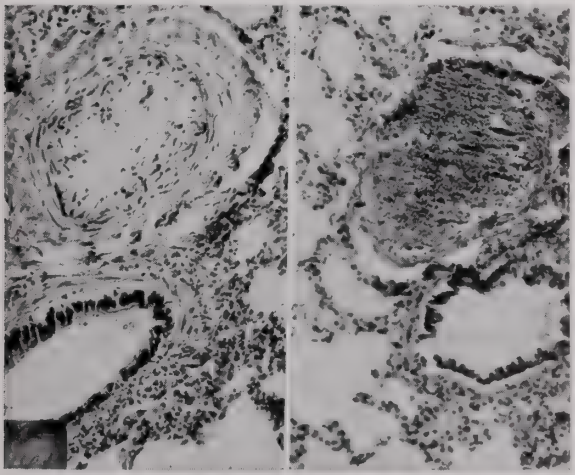

Fig. 1—Maturation of the Pulmonary Arteriole. *Left*: A small pulmonary arteriole in a newborn infant without cardiac or pulmonary disease. The thick-walled media is apparent. *Right*: A comparable pulmonary arteriole in a five-year-old child. Note the marked decrease in the thickness of the media. Small bronchioles confirm the comparable size and magnification of these pulmonary arterioles. Hematoxylin and eosin X135.

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*Read at the Regional Continuation Course on Chronic Respiratory Diseases in Children and Adolescents at the University of Minnesota, Minneapolis, September 17, 1968.

†Paul F. and Faith S. Dwan Professors of Pediatric Cardiology, University of Minnesota.

first few hours after birth; however, it remains above normal "adult" values because the pulmonary arteriolar media remains thick. It decreases in size gradually over the next six months and is accompanied by a fall in the pulmonary vascular resistance (Figure 1 *right* and Figure 2).

The congenital cardiac lesions discussed below may alter normal pulmonary vascular maturation in the following ways: (1) Maturation may be prevented; (2) Maturation may be delayed; (3) *Medial* hypertrophy and intimal proliferation may be superimposed at any point in the maturational process.

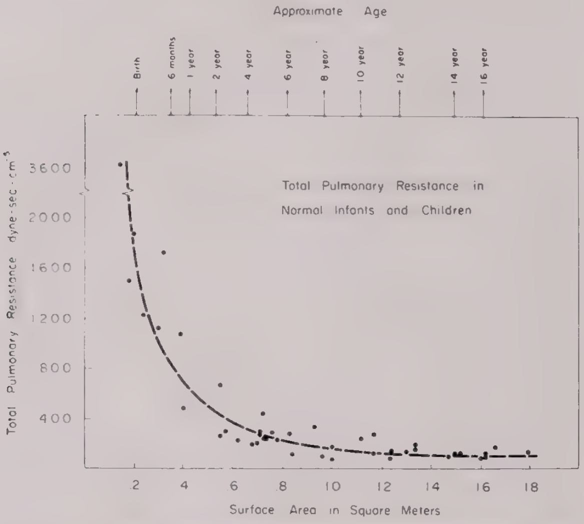

Fig. 2—Total pulmonary resistence as calculated from cardiac catheterization data in normal infants and children. Adapted from Lucas and associates.[3]

Obstruction to Pulmonary Venous Drainage

A classical example of pulmonary venous obstruction is mitral stenosis (Figure 3). Other responsible congenital defects include cor triatriatum, stenosis of individual pulmonary veins, supravalvular stenosing ring of the left atrium, total anomalous pulmonary venous connection with obstruction, mitral insufficiency, and any cause of left ventricular failure.[4] The common denominator of these left-sided obstructive lesions is elevated pressure in the pulmonary veins. The wall of the hypertensive pulmonary vein exhibits medial hypertrophy (Figure 4).

There are two major protective mechanisms which operate when pulmonary edema threatens life. The first is increased pulmonary lymphatic flow which has been demonstrated experimentally[5] and for which there is clear anatomic evidence of the form of gross dilatation of pulmonary lymphatics[6] (Figure 5). The second protective mechanism to minimize pulmonary edema is reflex constriction of the pulmonary arterioles (Figure 6). This results in a decrease in blood flow to the lungs until input and output are balanced. Pulmonary arteriolar constriction causes pulmonary hypertension, right ventricular hypertrophy, and

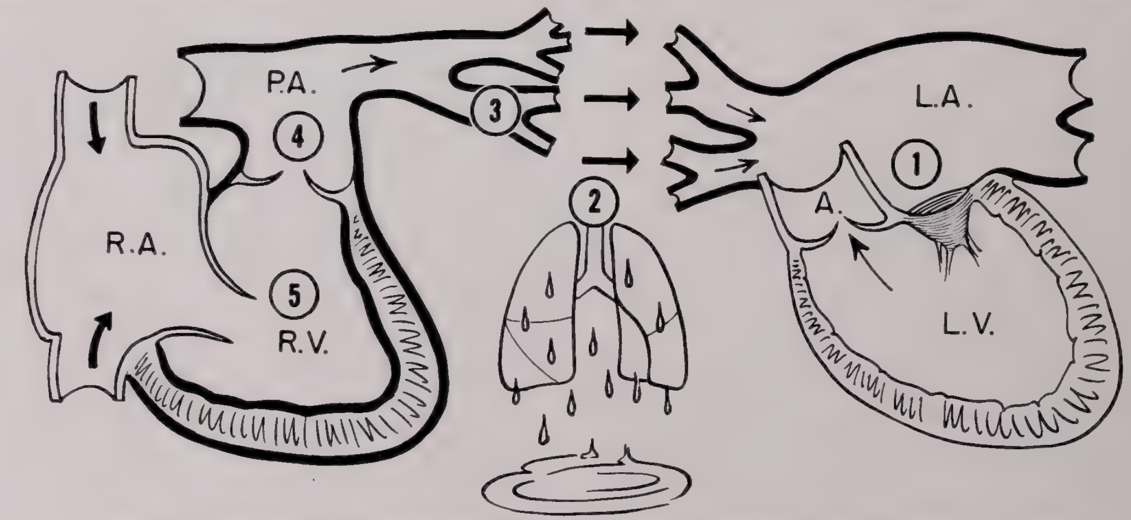

Fig. 3—Diagrammatic representation of hemodynamics in congenital mitral stenosis. Arrows represent the pulmonary vascular bed. Left atrial pressure is elevated (1) and is freely transmitted to the pulmonary capillary bed. Pulmonary capillary hydrostatic pressure exceeds osmotic pressure and pulmonary edema occurs (2). A compensatory mechanism to prevent pulmonary edema in constriction of pulmonary arterioles (3) which results in pulmonary hypertension (4) and may lead to right heart failure (5). From Lucas and Schmidt, Congenital Heart Disease in "Current Diagnosis", edited by Conn, Clohecy and Conn, W. B. Saunders Company, 1966. Reproduced by permission of the publishers.

in time right heart failure. Thus pulmonary venous obstruction profoundly alters the function of the pulmonary vascular bed and also results in intrinsic and extrinsic airway obstruction as will be discussed below.

Correction of the anatomic lesion producing pulmonary venous obstruction almost invariably results in return of the pulmonary vascular bed to normal and thus a normal hemodynamic state.

Increased Pulmonary Blood Flow, Normal Pulmonary Artery Pressure

The classic example of this hemodynamic situation is atrial septal defect. Other responsible defects include partial anomalous pulmonary venous connection, small ventricular septal defect and small patent ductus arteriosus. Maturation of the pulmonary vascular bed proceeds normally. At varying ages, but usually in the third or fourth decade of life, intimal proliferation occurs in the pulmonary arteriole. Resistance to pulmonary blood flow increases, pulmonary artery pressure rises, and the proliferative process progresses at an accelerating rate. As a consequence, the left to right shunt becomes balanced, then reverses. Symptoms of cor pulmonale appear and right heart failure may supervene. Intimal proliferation is not a reversible process. If it has progressed to the point of balancing the shunt, the pulmonary obstruction is then the factor limiting effective cardiac output. Repair of the cardiac defect is of no benefit in this circumstance.

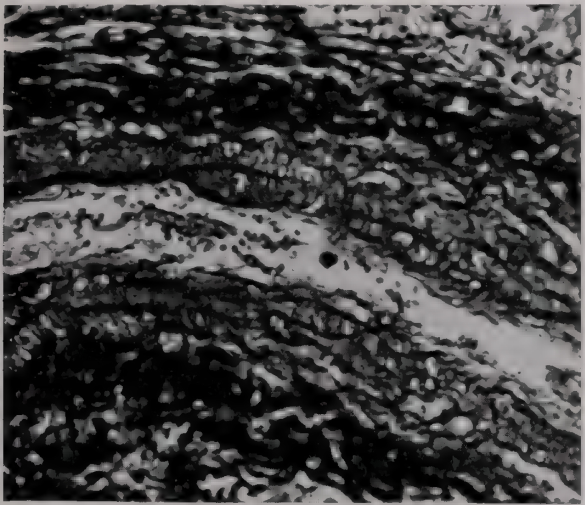

Fig. 4—Medial hypertrophy of a pulmonary vein in longitudinal section. The interdigitating elastic fibers identify it as a venous structure. Elastic tissue stain X 270. From Lucas and Associates.[6] Reproduced by permission of the American Academy of Pediatrics, Inc.

Increased Pulmonary Blood Flow, Elevated Pulmonary Artery Pressure

The common cause is large ventricular sep-

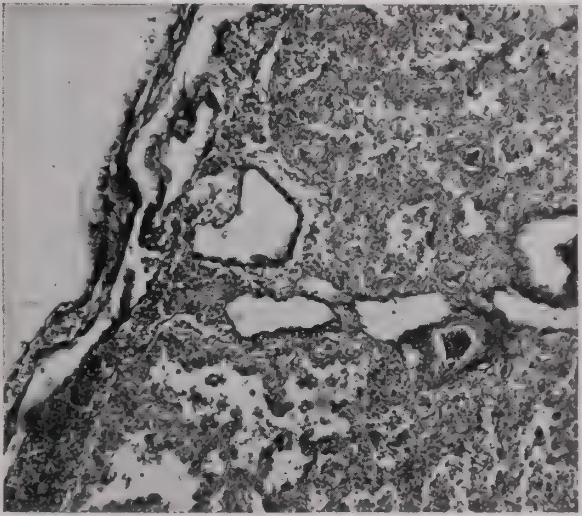

Fig. 5—Gross dilatation of pulmonary lymphatics in a child with pulmonary venous obstruction. The large dilated irregular lymphatic channels are seen under the pleura and in an interlobular septum. Hematoxylin and eosin X 25. From Lucas and Associates.[6] Reproduced by permission of the American Academy of Pediatrics, Inc.

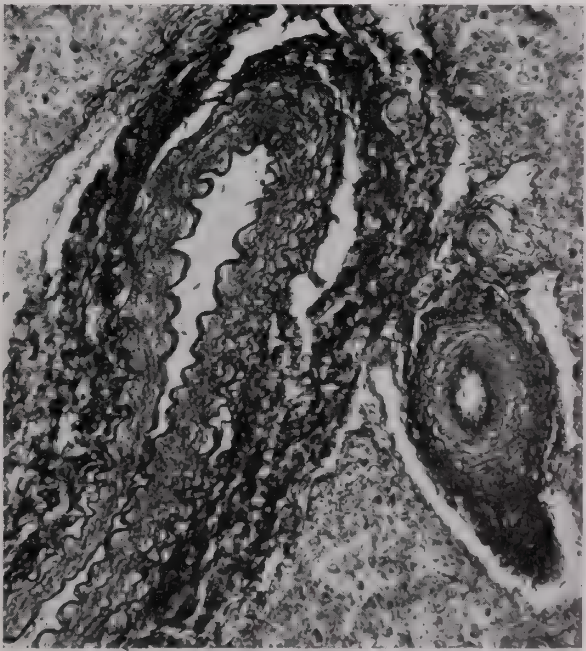

Fig. 6—Medial hypertrophy of pulmonary arterial vessels in a four-and-one-half-month-old child with pulmonary venous obstruction. There is medial hypertrophy of the large elastic artery, medium-sized muscular artery and several small arterioles. Elastic tissue stain X 135.

tal defect. Other defects resulting in this hemodynamic state are large patent ductus arteriosus, aortico-pulmonary window, truncus arteriosus, transposition of great vessels with ventricular septal defect, origin of both great vessels from the right ventricle without pulmonary stenosis, and single ventricle without pulmonary stenosis. Despite the similar hemodynamic stress, several different adaptations of the pulmonary vascular bed have been recognized.[7] Pulmonary vascular maturation may fail to occur; the high fetal pulmonary vascular resistance is maintained and pulmonary blood flow is minimized. Delayed maturation of the pulmonary vascular bed is a second response; pulmonary vascular resistance falls gradually, allowing adjustment of the hemodynamic system to increasing pulmonary blood flow. Pulmonary vascular bed maturation may also occur normally. This response allows massive pulmonary blood flow and is usually accompanied by severe congestive heart failure. In these latter patients, secondary medial hypertrophy usually develops.

As long as the alteration in the pulmonary arteriole is limited to hypertrophy of the media (Figure 7, left) the process is reversible, and surgical correction of the cardiac defect allows the pulmonary vascular bed to return to normal. On the other hand, intimal proliferation (Figure 7, right) is an irreversible phenomenon. Should this process progress to the point whereby the shunt is balanced, the irreversible pulmonary vascular lesions represent the limiting hemodynamic factor and cardiac surgery is of no benefit. These irreversible intimal changes may develop as early as the first year or as late as the third decade of life.

The differing responses of the pulmonary vascular bed to the similar stresses of high pulmonary blood flow and increased pulmonary pressure are presumably related to variability of pulmonary vascular reactivity in man.

Thrombotic and Embolic Complications

Bacterial Endocarditis

Patients with congenital cardiac disease have

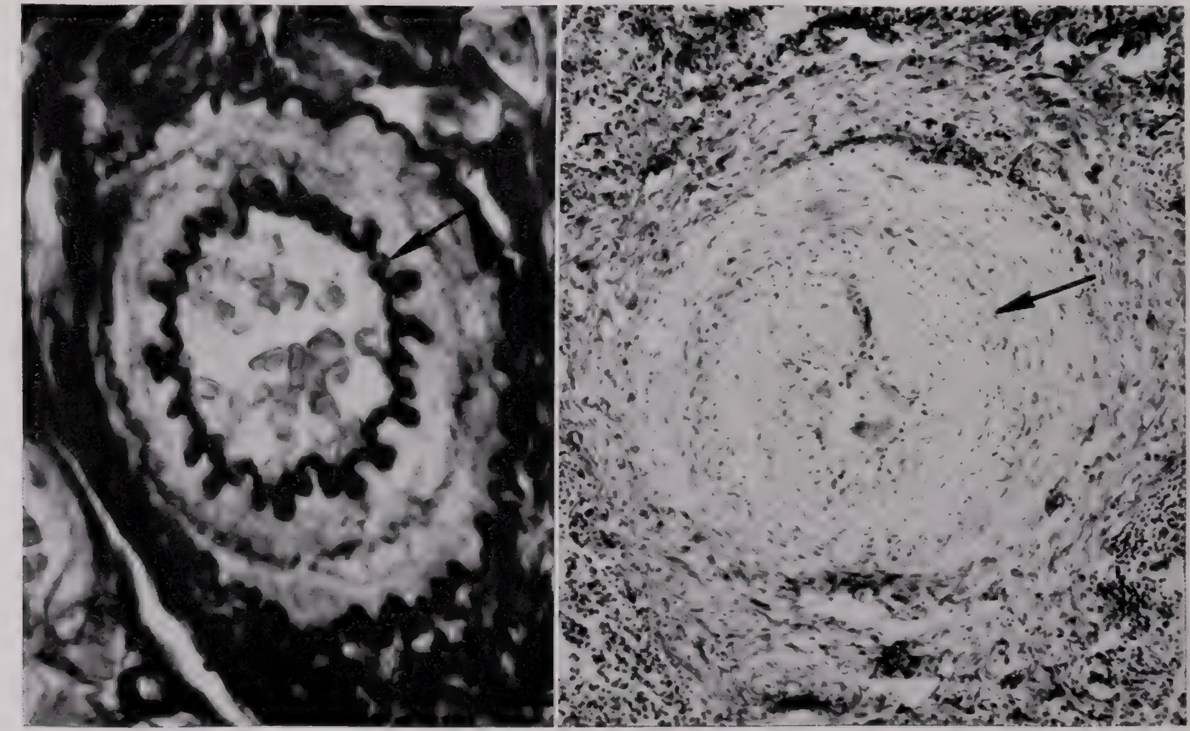

Fig. 7—Medial hypertrophy and intimal proliferation in the pulmonary arteriole in two patients with ventricular septal defect. The intimal elastic lamina (arrows) separates intima from media. *Left.* Pulmonary arteriole in a 20-month-old boy. Note significant medial hypertrophy and absence of intimal proliferation. Elastic tissue stain. *Right.* Pulmonary arteriole in a five-year-old boy. In addition to medial hypertrophy there is prominent intimal proliferation. Hematoxylin and eosin.

a predisposition to bacterial endocarditis; in patients with acquired valve disease endocarditis almost always involves a left-sided cardiac valve. On the other hand, bacterial endocarditis in congenital heart disease involves a right-sided valve or structure in the majority of cases. Thus, in congenital heart disease, when septic emboli occur they most often go to the lung. While these septic emboli may produce subtle pulmonary changes, they have not been incriminated as a cause for demonstrable permanent pulmonary disease. Our recent experience suggests that bacterial endocarditis may be a cause of significant, permanent pulmonary disability and is more common than appreciated. In the last year we have seen two patients with tetralogy of Fallot and bacterial endocarditis involving the right ventricular outflow tract who developed permanent and complete obstruction of the left pulmonary artery. The following case illustrates this complication of bacterial endocarditis.

Case Report

A nine-year-old girl with mild tetralogy of Fallot was admitted to the hospital six weeks after undergoing dental work. Six blood cultures grew Streptococcus viridans. A chest x-ray revealed an infiltrate in the left lung field which progressed to a wedge-shaped lesion extending to the surface of the lung (Figure 8). The bacterial endocarditis responded to penicillin therapy and a bacteriologic cure was achieved and maintained. At that time a lung scan (radioactive macro-aggregated albumin) revealed no evidence of blood flow to the left lung (Figure 9). Pulmonary arteriography was then performed and confirmed the absence of blood flow to the left lung. (Previous angiography had demonstrated a normal left pulmonary artery and normal blood flow to the left lung.) (Figure 10).

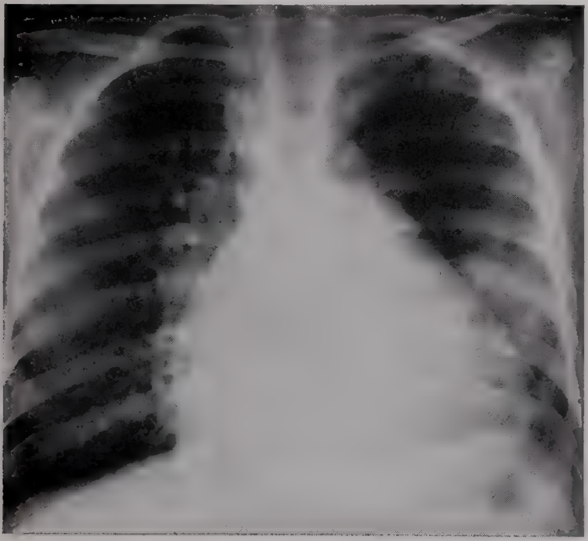

Fig. 8—Thoracic roentgenogram in a nine-year-old girl with tetralogy of Fallot, bacterial endocarditis and pulmonary embolus in the left lung. Note the wedge-shaped opacity extending to the pleural surface in the midleft lung field.

Correction of the intracardiac defect was performed without complication. The patient continues to have significant exercise intolerance. The left lung is non-functional.

Thrombosis Secondary To Decreased Pulmonary Blood Flow

When total pulmonary blood flow is diminished, velocity of blood flow through the lungs is decreased. Polycythemia, secondary to arterial desaturation, is also usual. As a result of these and possibly other factors, thrombosis may occur in pulmonary vessels. An occasional patient with tetralogy of Fallot is so affected. In these patients the pulmonary vascular obstruction may not be apparent preoperatively since pulmonary blood flow is low. When the vascular obstruction is unmasked by corrective surgery, adequate pulmonary blood flow is not attainable and pulmonary hypertension and right heart failure may follow.

Anatomic Features Resulting in Airway Obstruction

In infants with congenital cardiac disease emphysema and atelectasis as a result of airway obstruction are commonly seen. In these

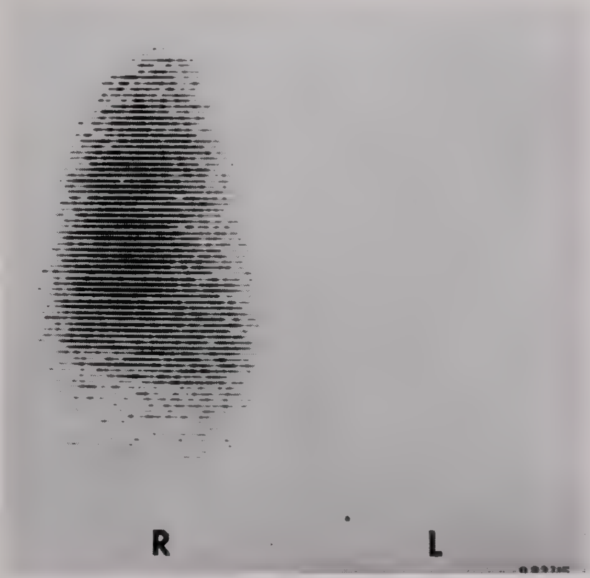

Fig. 9—Lung scan four weeks following the roentgenogram depicted in Figure 8. There is no evidence of blood flow to the left lung (L). The scan of the right lung (R) appears normal.

patients airway obstruction may be due to compression of the bronchi by adjacent structures or by intraluminal bronchial narrowing, or by both.[8]

Airway Obstruction Caused by External Compression

External bronchial compression is most often the result of distended, hypertensive pulmonary arteries. Pulmonary hypertension may be a manifestation of certain left-to-right shunts or of pulmonary venous obstruction. The relationships of the pulmonary arteries to the main stem bronchi are seen in Figure 11. As the left pulmonary artery crosses the left main stem bronchus from front to back it may compress the superior aspect of the left main stem bronchus. In addition, the left upper bronchus may be compressed by the inelastic C-shaped arterial structure formed by the branch of the pulmonary artery leading to the left lower lobe as it crosses behind the left upper bronchus and then descends. A third site which shows a predilection for obstruction is the bronchus intermedius which is compressed as the right pulmonary artery crosses over it from front to back.

Bronchial compression due to enlarged, hypertensive pulmonary arteries is intensified when left atrial enlargement is also associated, since the left atrium lies immediately subjacent to the bronchial bifurcation and its enlargement results in an upward pressure on the inferior aspect of both major bronchi, particularly the left. The pulmonary arteries limit the upward mobility of the bronchi. Thus the bronchi are caught in a hemodynamic vise, the upper jaw consisting of the distended hypertensive pulmonary artery and the lower jaw, the enlarged left atrium.[8]

The cardiac defects resulting in a combination of left atrial enlargement and dilated hypertensive pulmonary arteries include ventricular septal defect, patent ductus arteriosus, atrioventricular canal, transposition of the great vessels and the various causes of pulmonary venous obstruction.

If bronchial obstruction is incomplete, lobar emphysema occurs. More commonly, obstruction is complete and produces atelectasis of the obstructed lobe.

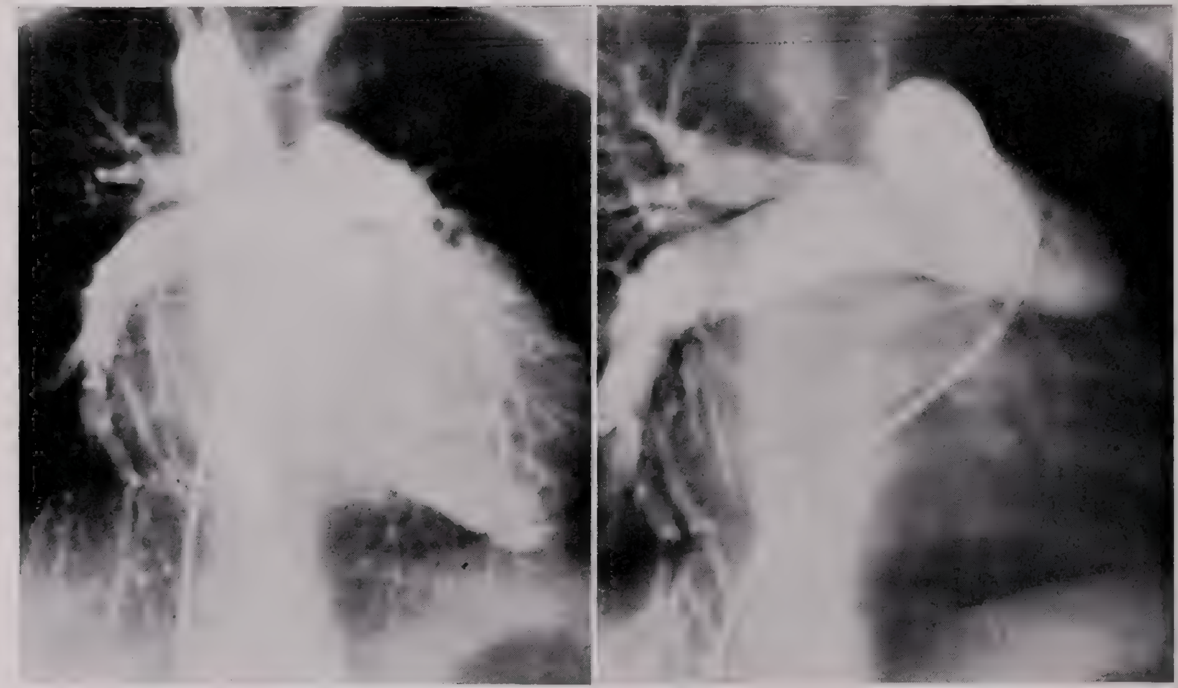

Fig. 10—Angiograms in the patient shown in Figures 7, 8 and 9. *Left:* Right ventriculogram obtained prior to the episode of bacterial endocarditis. There is normal filling of both right and left pulmonary arteries. *Right*: Pulmonary arteriogram obtained subsequent to the bacterial endocarditis and the infiltrative process noted in the left lung. Main pulmonary artery and right pulmonary artery fill normally. There is no opaque dye entering the left pulmonary or the left lung field.

Intrinsic Airway Obstruction

Multiple factors may contribute to intraluminal bronchial narrowing. Since the bronchial veins communicate with the pulmonary venous system, those conditions resulting in elevation of pulmonary venous pressure will also result in bronchial venous hypertension. This in turn leads to increased bronchial secretions and edema of the bronchial mucosa.

Infection is a common complication in patients with increased pulmonary blood flow, atelectasis and congestive cardiac failure. Infection also results in mucosal edema and excessive secretions. When dehydration occurs, a more viscous secretion increases the likelihood for intrinsic obstruction.

These intrinsic factors may be the sole cause of obstruction or may act in conjunction with extrinsic compression of the bronchi to result in a critical decrease in intraluminal diameter.

Predilection of Infants to Pulmonary Complications

The incidence of pulmonary complications in congenital cardiac disease is highest in the first year of life. Alterations in the pulmonary vascular bed contribute to this age incidence.

Other pulmonary factors also favor a high incidence of pulmonary complications in infants. Resistance to air flow through a bronchus is proportional to $1/r^4$ ($r =$ radius of bronchial lumen). Thus, in the infant, the initially small bronchial radius may be reduced to the critical point of obstruction by relatively modest intrinsic or extrinsic forces. As growth occurs, a greater decrease in luminal size is required before the bronchus is obstructed. Secondly, the soft pliable bronchial cartilage in the infant is readily deformed by extrinsic pressure. Finally, the pores of Kohn in the infant are poorly developed. Bronchial obstruction is thus more likely to result in atelectasis since collateral ventilation is prevented.

TABLE

Pulmonary Complications of Congenital Cardiac Disease

- I. Alterations in the Pulmonary Vascular Bed
  - A) Obstruction to pulmonary venous drainage.
  - B) Increased pulmonary blood flow; normal pulmonary artery pressure.
  - C) Increased pulmonary blood flow; increased pulmonary artery pressure.
- II. Thrombotic and Embolic Complications
  - A) Bacterial endocarditis (involving right-sided structures).
  - B) Thrombosis secondary to decreased pulmonary blood flow.
- III. Airway Obstruction
  - A) External bronchial compression.
  - B) Intrinsic bronchial obstruction.

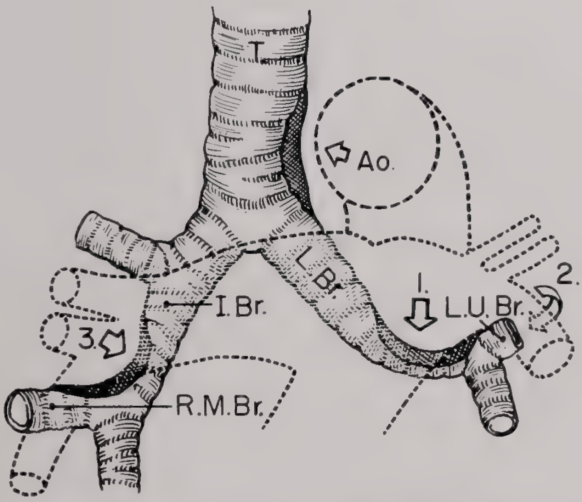

Fig. 11—Sites of bronchial compression due to enlarged, hypertensive pulmonary arteries. The dotted lines represent the more anterior pulmonary arteries. 1) Left pulmonary artery compresses the superior portion of the left bronchus (L. BR.) as it crosses over the bronchus from front to back. 2) The arterial branch to the left lower lobe crosses behind the left upper bronchus (L. U. BR.) before it descends. The left upper bronchus is thus caught in a C-shaped vascular sling and may be obstructed. 3) Right pulmonary artery crosses over the bronchus intermedius (I. BR.) and the artery branches to the right lower lobe cross behind the right middle lobe bronchus (R.M.Br.) Compression of the bronchus intermedius more often results in atelectasis of the right middle lobe; but the right lower lobe may be obstructed as well. The left atrium lies immediately subjacent to the tracheal bifurcation. When the left atrium enlarges, it pushes the bronchi, particularly the left bronchus, upward and intensifies the obstructive effect of the enlarged pulmonary arteries. Ao=aorta. T=trachea. From Stanger and Associates.[8] Reproduced with permission of the American Academy of Pediatrics, Inc.

Comment

As the heart and lung are intimately bound together anatomically and hemodynamically so must they be inseparable in our consideration of the child with congenital cardiac disease.

Infants and children with cardiac disease may present with pulmonary problems such as pneumonia, atelectasis, lobar emphysema or what appears to be diffuse bronchiolitis. Thus the differential diagnosis in the infant or child with pulmonary symptoms must include congenital cardiac disease.

Further, successful management of the infant or child with congenital heart disease depends on the early recognition, prompt treatment and, ultimately, prevention of the respiratory complications which are so common. In the infant in particular, pulmonary complications limit our success in preoperative and postoperative management. Every effort must be expended to improve our treatment in the acute respiratory problems encountered in the infant with congenital cardiac disease.

Finally, while we are well aware of the acute respiratory problems in congenital cardiac disease, we know little of the long-term pulmonary sequelae in these patients. The knowledge that intimal proliferation in the pulmonary arteriole is an irreversible process has influenced us to lower the age of operative intervention in a variety of cardiac defects in order to prevent it. However, the long-term sequelae of chronic atelectasis, lobar emphysema, bacterial endocarditis and pulmonary arterial thrombosis are not known. When we acquire better knowledge of these chronic pulmonary processes, further changes in our treatment philosophy in the patients with congenital heart disease may be in order.

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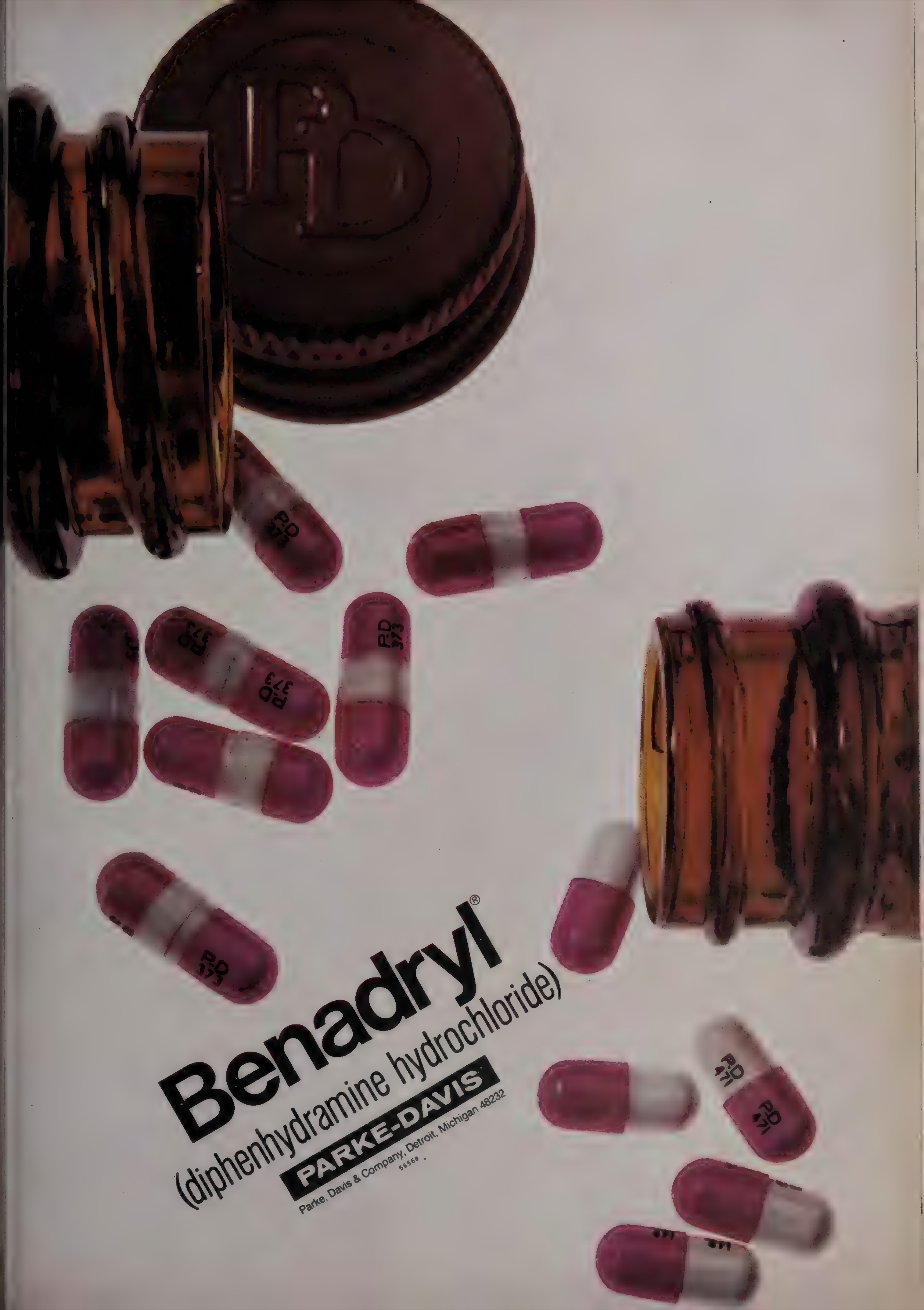
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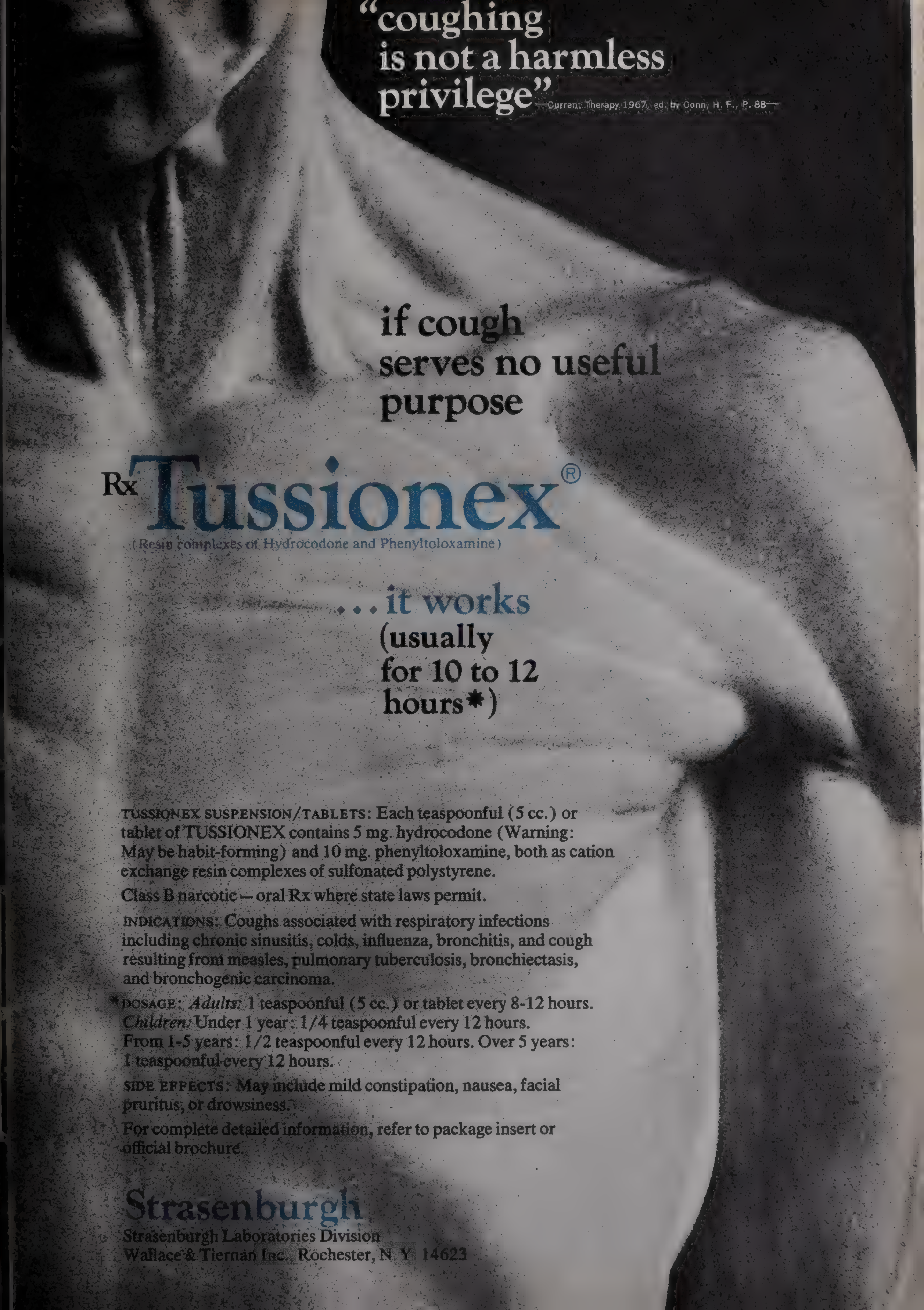

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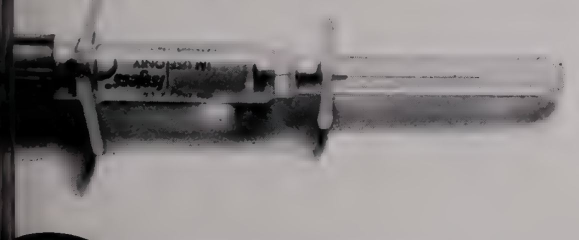

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Continued to page 1442

Cystic Fibrosis*

Current Theories Concerning the Pathogenesis*

ALEXANDER SPOCK, M.D.[†]
Durham, North Carolina

Cystic fibrosis is a generalized inherited disease of children, adolescents and young adults in which there is a dysfunction of all or most of the exocrine glands. Clinical manifestations of this disease include chronic pulmonary disease, pancreatic insufficiency, and elevated sweat electrolytes. A puzzling feature of cystic fibrosis is the marked variability in the severity of the disease in different patients, even within a single family.

The basic defect in cystic fibrosis is not known. Numerous hypotheses have been presented in an attempt to provide a unifying concept in order to explain the electrolyte and mucopolysaccharide abnormalities. These hypotheses are well summarized in several recent reviews.[1-4]

An attempt will be made to correlate this new information with the four most commonly accepted theories for the pathogenesis of cystic fibrosis. These four theories are: (1) abnormal secretions; (2) autonomic dysfunction; (3) humoral abnormality; and (4) ion transport dysfunction.

Abnormal Secretions

The abnormal secretions which occur in patients with cystic fibrosis have been recognized as the basic pathological lesion resulting in clinical symptoms due to bronchial and pancreatic obstruction. The increased viscosity of these secretions has been attributed to an *increased fucose and decreased sialic acid* levels of the glycoproteins[5] and more recently to a complex formed by the glycoprotein and calcium,[6] though there has been no delineation of the underlying biochemical defect.

Reid[7] has shown that prior to pulmonary infections, patients with cystic fibrosis have normal bronchial glands and secretions. However, with infections, hypertrophy of the bronchial glands occurs, resulting in an increased production of sulfamucins and decreased concentration or even elimination of the sialomucins.

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*Read at the Regional Continuation Course on Chronic Respiratory Diseases in Children and Adolescents at the University of Minnesota, Minneapolis, September 17, 1968.

†Duke University Medical Center, Durham.

In 1968 Danes and Bearn[8] demonstrated that fibroblasts from skin biopsies of patients with cystic fibrosis stain metachromatically due to the *abnormal presence of a cytoplasmic substance*. Even more remarkably, heterozygous* relatives have similar changes in the fibroblasts. Danes[9] reports that the staining abnormalities in cystic fibrosis are of two types. In type I, the metachromasia appears diffusely throughout the cytoplasm as vacuoles; in type II, the fibroblasts show diffuse granular metachromasia. The types are genetically consistent, as in every family studied the patient and parents fall in the same class.

The metachromatic staining of fibroblasts is thought to represent acid mucopolysaccharides. Matalon and Dorfman[10] studied the acid mucopolysaccharide content of the culture fibroblasts and noted that the *total amount of polysaccharide* isolated from fibroblasts in a patient with cystic fibrosis was approximately eight to 10 times that present in normal fibroblasts. The acid mucopolysaccharide fraction contained high uronic acid, dermatan sulfate, and chondroitin sulfate 4/6 levels; however, these levels closely paralleled the distribution of these mucopolysaccharides in normal cells. Danes[9] also observed that cells of type II have an increased intracellular mucopolysaccharide content. In contrast, type I cells have no increase in intracellular mucopolysaccharide content.

Metachromatic staining has also been demonstrated in cultured white blood cells from patients with cystic fibrosis[11] and fibroblasts obtained from amniotic fluid of mothers known to have children with cystic fibrosis.[12] Since the metachromatic staining technique does not differentiate the heterozygote from the homozygote, it can not be utilized to establish the diagnosis of cystic fibrosis. Furthermore, as the metachromatic substance detected in cystic fibrosis is also seen in many mucopolysaccharides, this technique should at the present time be utilized with appropriate caution for genetic counseling.

The exact reason for the accumulation of the mucopolysaccharides within fibroblasts obtained from patients with cystic fibrosis as well as from the heterozygote is not known. Possible explanations for this occurrence include: a defect in the cell membrane, a defect in the lysozymes or a specific enzyme within the lysozyme which normally break down mucopolysaccharides, or an increased synthesis due to lack of an inhibitor.

Autonomic Dysfunction

During the past two decades numerous studies have implicated the autonomic system in the pathogenesis of cystic fibrosis.[13] The exocrine glands are innervated and controlled in their secretory activity by the autonomic nervous system, and the increased parotid secretory rate noted in patients with cystic fibrosis probably indicates *hyperactivity of the autonomic nervous system*. Eyeman et al.[14] observed an increased concentration of acetylcholine in the sweat of patients with cystic fibrosis. Chernick and Barbero[15] demonstrated that changes similar to those found in the submaxillary saliva of patients with cystic fibrosis can be induced by parasympathomimetic stimulation in normal children. In addition, the adrenergic blocking agent, guanethedine, clears the turbidity of this secretion which is characteristic of patients with cystic fibrosis. The change in turbidity was the result of a decrease in the organic constituents of the saliva; the guanethidine had little effect upon the ionic components. The action of guanethidine in reversing the turbidity associated with these secretions probably indicates that the secretory abnormality in cystic fibrosis is not of a propressively irreversible type.

Attempts to reproduce cystic fibrosis by chronic administration of pilocarpine or atropine have failed to reproduce the syndrome of cystic fibrosis. Structural and functional studies of the autonomic nervous system have failed to produce an explanation of the disease, and the various abnormalities suggestive of autonomic dysfunction in cystic fibrosis cannot be adequately correlated with each other. Barbero[16] postulates that it is unlikely that a generalized disturbance of the autonomic nervous system occurs in cystic fibrosis. It is more likely that the site of the defect is at the neuroglandular junction or within the secretory end organ itself.

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*See Test Your Word Score Page 1401.

Humoral Abnormality

The possibility that cystic fibrosis has as its basic defect the production of either *abnormal hormone or increased concentration* of a normally occurring hormone capable of stimulating exocrine tissue has been studied only recently. The evidence for this theory is based primarily on the results of Spock et al.,[17] who demonstrated a serum factor in patients with cystic fibrosis and in parents of children with cystic fibrosis.

Utilizing a bio-assay method, Spock et al.[17] observed that serum from patients with cystic fibrosis disorganized the ciliary rhythm in explants of respiratory epithelium. This effect was absent from the serum of patients having a variety of diseases with clinical features similar to those seen in cystic fibrosis. The serum factor was also detected in the parents of children with cystic fibrosis; however, the concentration of the factor was lower. The serum factor was heat-labile, nondialysable and, upon chromatographic examination, appeared with the macroglobulin fraction as well as between the gamma globulin and albumin peaks. The mechanism by which the serum factor produces disorganization of the ciliary beat is not yet understood. However, these authors postulated that the macromolecules in the serum may alter transport of electrolytes across the cell membrane, thereby producing change in the action potential within the cell with subsequent disorganization of the ciliary beat. This study also noted that the ciliary activity of explants from patients with cystic fibrosis was normal when not exposed to the patient's serum.

Verification of the above mentioned results has been made by Bowman et al.[18] who noted that serum from patients with cystic fibrosis and heterozygotes produced cessation of ciliary activity of oyster gills within 35 minutes. In contrast, sera from only two of 64 individuals without cystic fibrosis inhibited ciliary activity within this time. This serum factor shares properties in common with the serum factor noted by Spock et al.[17]

The humoral theory for cystic fibrosis does not explain such observations as the presence of the disease in the fetus, occurrence of a generalized and varied disease due to a single hormone, and restriction of humoral influence only to exocrine function.

Ion Transport Dysfunction

The sweat electrolyte abnormality consisting of *elevated sodium and chloride* levels is present in virtually all patients with cystic fibrosis. Using micropuncture techniques, Schulz[19] has demonstrated that this abnormality is the result of a defect in the reabsorption of sodium chloride by the duct of the sweat gland. The sweat gland does not show any anatomical or enzymatic defects in the glands of patients with cystic fibrosis to account for dysfunction of the gland.

In 1967 Mangos and McSherry[20] noted that when saliva or sweat from patients with cystic fibrosis was introduced by retrograde injection into the parotid glands of rats, marked inhibition of sodium reabsorption occurred; but retrograde perfusion with normal saliva or sweat from normal children did not affect the rate of sodium reabsorption. The effect was also shown not to be due to inhibition of the ATPase enzyme. Subsequent studies by Mangos[21] have shown that inhibition of sodium reabsorption was also produced by retrograde injection into the parotid glands of rats of positively charged substances, e.g., protamine sulfate, poly-L-lysine. In contrast, when the saliva of patients with cystic fibrosis was mixed with a negatively charged substance (heparin or polyglutanic acid) and injected in the same manner, the sodium transport inhibitory effect of the saliva practically disappeared.

Mangos[22] has studied the effect of euglobulin from patients with cystic fibrosis upon the rat parotid gland system. The euglobulin did not cause any inhibition of sodium reabsorption; however, fractionation of the euglobulin disclosed a small polypeptide capable of producing marked inhibition of sodium reabsorption. This fraction of serum was also capable of producing disorganization of the ciliary beat in the bio-assay system. Mangos, McSherry, Benke and Spock[23] have also demonstrated that rats treated with 5 mg of isoproterenol SO_4 for three weeks developed marked enlargement of the salivary glands, quantitative and qualitative changes in the excretion of basic macromolecules in parotid saliva, increased sodium concentrations in the parotid saliva, and appearance of a factor in the serum of these rats resulting in ciliary dyskinesis.

A red-cell transport defect in patients with cystic fibrosis and their parents was recently reported by Balfe, Cole and Welt.[24] This investigation demonstrated a diminished active transport of sodium in the erythrocytes of patients with cystic fibrosis. Of special significance is the marked decrease in pump II in the parents. Previous studies[25] noted the sodium pump in erythrocytes to be functioning normally.

The theory of ion-membrane dysfunction in cystic fibrosis may unravel the confusion concerning the basic defect seen in this disease; however, as of today our knowledge concerning cellular membrane structure and transport is too limited to provide such a solution.

Summary

The diverse and at times conflicting statements concerning the pathogenesis of cystic fibrosis presented in this paper reaffirm our inability to identify the basic defect in cystic fibrosis. However, with currently available evidence the following hypothesis can be proposed. A humoral substance present in the body fluids of patients with cystic fibrosis attaches to or acts upon the membrane surface of cells of the exocrine gland. The interaction of the humoral substance with the cell results in increased metabolic activity within the cell with subsequent alteration of cell membrane permeability and increased protein and mucopolysaccharide synthesis.

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Cystic Fibrosis*

Pathogenesis of the Pulmonary Lesion

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THE PULMONARY COMPLICATIONS in cystic fibrosis are considered to be on an obstructive basis due to viscid materials in the airways, with dilatation and infection occurring in the airways which are occluded. The chronic obstruction increases susceptibility to infections, and metaplasia of bronchial and tracheal epithelium occurs.

In the earliest lesions, Hemophilus influenzae, Klebsiella pneumoniae and Staphylococcus aureus are often found. As the lesion progresses, Staphylococcus aureus is more consistently present. Pseudomonas aeruginosa eventually appears and may become the only pathogen.

Marked variability of the manifestation of cystic fibrosis occurs in the lungs and in many other organs: the pancreas, liver, salivary glands. The glandular organs show a ductular obstructive process. Engorgement occurs in the salivary, bronchial, duodenal and rectal mucous glands, suggesting the pathogenic role of mucus abnormality. The excess salinity of the sweat, however, suggests that the defect is also in the secretory process and not limited to the mucous glands.

Later stages of development of the pulmonary lesion involve bronchiectasis, bronchitis shading into pneumonia, atelectasis followed by pneumonia or abcess, emphysema, pulmonary fibrosis, and at times cavitation and hemorrhage. The vital capacity gradually diminishes, but an excessive proportion of residual volume occurs. The terminal event is usually anoxic failure, with a heart burdened by excessive pulmonary artery pressure. Anoxia is finally precipitated by accumulation of mucopurulent material in the respiratory tract. This is accelerated pre-terminally with failure of effective coughing and carbon-dioxide narcosis. This sequence of events is a classical concept in cystic fibrosis.

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*Read at the Regional Continuation Course on Chronic Respiratory Diseases in Children and Adolescents at the University of Minnesota, Minneapolis, September 17, 1968.

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In order to get a look at an early pulmonary lesion, a 1948 case was recalled. A boy died at the age of eight years due to hemorrhage from esophageal varices. Death was complicated by hepatic failure and cerebral edema. He had complete pancreatic deficiency and hepatic cirrhosis with little or no clinical evidence of pulmonary involvement, although pulmonary function tests had not been done.

This original protocol stated that there was slight but definite evidence of pulmonary involvement, mainly bronchiolar. Grossly, the bronchi were free of secretion. Histologically, the tracheal epithelium was intact, but the submucosa was infiltrated with a moderate number of plasma cells. The bronchi showed intact columnar epithelium; smaller bronchi were partially filled with exudate which contained some mucoprotein, as indicated by a PAS stain (Figure 1), and there was slight inflammatory reaction around these small bronchi. Bronchioles showed more filling with mucopurulent secretion and more inflammatory reaction in the surrounding area (Figure 2). There were some areas of thickened alveolar walls with inflammatory reaction, (interstitial pneumonitis) and some disruption of alveolar walls as emphysema.

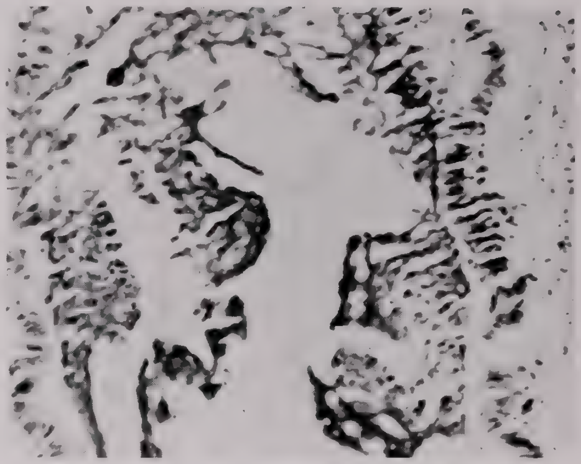
Fig. 1—Small bronchial branch showing relatively acellular exudate with mucoprotein stained by PAS.

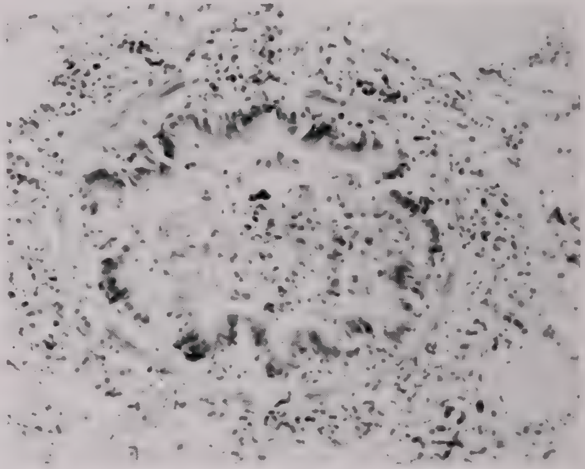
Fig. 2—Bronchiole filled with mucopurulent exudate and surrounded by inflammatory reaction. The epithelium is intact. H & E.

Summary

The first step in the muco-obstruction of the bronchial tree in cystic fibrosis is in the bronchiole. This tends to peripheral bronchiolar infections and peripheral air trapping and explains the tendency toward emphysema and atelectasis observed in infants with cystic fibrosis.

Acknowledgment: This study was supported in part, by the National Cystic Fibrosis Research Foundation.

The Mining-Camp Medic

A mining-camp doctor was accustomed to long hours and long miles. A Sacramento physician started Sunday, June 21, 1868, at 4 A.M. Before he went to bed that night between 10 and 11 P.M., he had worn out three horses to make a total of 100 visits to 87 different families. Only the toughest horses could stand a dedicated doctor's pace. To get such a horse Dr. Gardiner tamed a wild bronco with whiskey and mash until it was so docile it followed him about as if it were a dog. When a drunk threatened to shoot his horse one day, the doc pulled a gun on him.*

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*Richard Dunlop: Doctors of the American Frontier, 1965.

Women are just like elephants to me; I like to look at them, but I wouldn't want one.—Frank McKinney Hubbard

Chronic Lung Disease*

Clinical Evaluation of the Child

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PULMONARY FUNCTION TESTING begins with a clinical quantitative approach to the child during the physical examination. No laboratory is required for its performance or interpretation. It lends itself easily to serial use in the same patient; in fact, it is of greatest value when routinely employed on each clinic visit. It is painless and calls for no effort from the child. It is independent of the variability produced by an examiner's bias because it is objective. Since only minimal cooperation is required, it is applicable throughout all or most of childhood. Finally, it is an index of certain aspects of pulmonary disease that may be impossible to measure directly, such as obstruction, restriction, and destruction.

In spite of these advantages, the application of an emphatically quantitative physical examination calls for a mind that enjoys precision and delights in maintaining careful charts in a patient's record. Other minds will prefer more traditional qualitative methods. Perhaps even more, quantitation appeals to physicians who treat children with chronic lung disease, such as asthma or cystic fibrosis, because it gives them additional objective evidence of the course of each child's disease. Thus, these measures probably have diagnostic, therapeutic, and prognostic values.

Chronic Cough

One significant criterion for chronic pulmonary disease could be whether a child coughs at some time every day for three months. He then has, by definition, chronic pulmonary disease. Cough was selected because it is a very common sign or symptom of lung disease. Admittedly, there may be disease without cough, but cough is a very good way of locating a large group of patients with prolonged pulmonary disease. If an individual coughs even once, it is a sign of abnormality, since a cough is always a reaction to some insulting effect. In the evaluation of any child with cough, three quantitative approaches concern us: respiratory rate, thoracic depth and width, and two diameters of the left index finger. Tachypnea* will be considered an index of restriction; thoracic deformity an index of obstruction, and finger clubbing an index of destruction within the lungs. Let us see if dividing children who cough into these subcategories will allow more complete evaluation, both diagnostically and prognostically.

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*Read at the Regional Continuation Course on Chronic Respiratory Diseases in Children and Adolescents at the University of Minnesota, Minneapolis, September 17, 1968.

†From the Section of Pulmonary Diseases, Department of Pediatrics, Tulane University School of Medicine, New Orleans. Supported in part by a Center Grant from the National Cystic Fibrosis Research Foundation, by a Research Grant from the U. S. Public Health Service, National Institute of Arthritis and Metabolic Disease (No. 1 RO1 AM12752-01), and by a contract from the Chronic Respiratory Diseases Control Program of the Public Health Service, Department of Health, Education and Welfare (No. CCD-69-50). Views expressed by the authors are not necessarily those of the Public Health Service.

General Types of Pulmonary Disease

Restrictive Lung Disease

One of the oldest tests of pulmonary function is a well counted *respiratory rate*. We cannot take a crying, restless, or even anxious child, and use a rate counted on him for this type of test. Ideally, we need a tranquil child, perhaps sitting or sleeping in his mother's lap. Also, because of slight variations in the rhythmicity of the respiratory rate, we have to count for one, two or three minutes, taking the average count per minute.

One of the characteristic physical findings in restrictive lung disease is fast, shallow respirations: tachypnea and hypopnea. Stiff lungs require greater than normal work by the muscles of respiration; this work can be minimized by shifting from a normal breathing pattern to a faster and shallower one.

It follows that the respiratory rate becomes an index of restrictive lung disease. Other causes of tachypnea must be ruled out or otherwise interpreted: age, fever, anemia, thyroid disease, exercise, anxiety, and shock. The faster the rate, the stiffer the lungs; the stiffer the lungs, the greater the restrictive disease.

The term "restrictive" implies space-occupation: lobar pneumonia fills alveoli, so that they can no longer share in the gas-exchange function of the lungs; a large pleural effusion or pneumothorax compresses and "restricts" the lung from the outside; neuromuscular disease or lobectomy "restricts" lung function by limiting ability to ventilate. The diagnosis of restrictive disease depends on history, physical examination, and radiography; it is confirmed by pulmonary function testing which usually indicates a decreased vital capacity and frequently a stiffer, less compliant lung, one that requires a greater pressure change acting on it to produce a given change of volume.

Obstructive Lung Disease

Obstructive lung disease, an almost self-explanatory term, is the sum of effects resulting from the fact that the airway at one or more points lacks normal diameters and that therefore the to-and-fro movement of tidal volume is variably impeded. The causes of obstruction may be intraluminal (mucus, pus, foreign body), mural (bronchospasm, edema, inflammation), or extrabronchial (vascular or nodal compression). Regardless of its cause, obstruction makes necessary greater than normal inspiratory and expiratory pressures in order to maintain ventilation. Asthma, bronchiolitis, and cystic fibrosis produce prominent and more or less diffuse obstruction, affecting many bronchi and bronchioles.

Physical findings of obstruction include wheezing, various types of cough, prolongation of expiration, and retractions or bulging of intercostal spaces.

It has long been recognized that chronic obstructive lung disease of certain types (obstructive emphysema in adults, asthma and cystic fibrosis at all ages) is associated with a characteristic thoracic deformity, called "barrel chest," in which thoracic anteroposterior diameter is markedly increased. This effect is best explained as an application of Pascal's principle,[1] which predicts that a malleable nonspherical gas or fluid-filled object will approach a sphere as pressure within it is increased. (A simple example of Pascal's principle is the progressive obliteration of the ears and nose of a "Mickey Mouse" balloon by progressive inflation. With increasing pressure such a balloon ultimately assumes a perfect sphere, if it does not burst.) It follows that any lung disease that increases expiratory intrathoracic pressure will deform the chest and that the more severe the obstruction and the longer its duration, the greater will be the deformity and the more spherical the thorax. Accurate measurement of thoracic diameters facilitates early recognition of deformity and documents trends resulting from natural variations in disease severity or the effects of therapy.

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*See Test Your Word Score Page 1401.

Destructive Lung Disease

"Destructive" lung disease is more of a pathological concept than a physiological one. The classical example of destructive lung disease in childhood is bronchiectasis, whether it be secondary to the atelectasis produced by a foreign body or to that produced by mucous plugging in cystic fibrosis. In either case, the destructive process begins with bronchial obstruction and is followed by atelectasis and pyogenic infection. The end results are saccular bronchial dilatation, bronchorrhea with productive cough, diminished ventilation, and varying degrees of digital clubbing. Other types of destructive lung disease, such as obstructive emphysema and reinfection tuberculosis, do not occur to any significant degree during childhood.

Clubbing may be used as a general measure of destructive lung disease, provided one rules out non-pulmonary and non-destructive pulmonary diseases associated with it. Although it occurs in benign idiopathic instances, occasionally hereditary, such examples are rare. It is consistently seen in congenital cyanotic heart disease and in congenital pulmonary arteriovenous anastomoses. It may occur in biliary cirrhosis, chronic ulcerative colitis, and subacute bacterial endocarditis.

No case is made here for the *specificity* of clubbing as a parameter of destructive lung disease. Furthermore, once the association has been made with a disease, such as cystic fibrosis, something about the extent and the severity of the lung disease in that patient may be related to the degree of clubbing in a way not completely understood. In any event, a method of quantitating clubbing is useful in following children with "destructive" lung disease such as cystic fibrosis. Its appearance in an "asthmatic" child should arouse suspicion of the accuracy of the diagnosis, since it rarely appears in uncomplicated asthmatic patients, regardless of the severity or chronicity of their disease.

Limits of Normality

Serial Measurements

One of the inevitable problems with objective measurements is not so much what the expected or average value is for an individual but rather how much variability or "scatter" may exist about the expected value and still be considered "normal." Most measurements in childhood normally vary with sex, age, height, or weight, which are then often called independent variables. All pediatricians are familiar with boys' and girls' charts for height and weight, which are usually plotted as a function of the independent variable, age. Limits of normality are calculated either in percentile or standard deviation units. Regardless of the choice, it is clear that the farther an observed value falls from the expected mean value, the greater its chance of being abnormal.

The above holds for a single observation, such as the first time weight is recorded on a patient. With serial measurements on the same normal individual, one soon learns that the intra-individual variability is considerably less than that of the whole normal population. Each subject "seeks his own level" in the normal population. Changes of a few percentile points or one standard deviation may then be very significant. Hence one sees the value of frequently repeated determinations on the same patient.

The Growth Factor

The problem here is how to separate the effects of growth from those of disease. For most pulmonary function tests in children it has been found that height is usually the most satisfactory independent variable (the one minimizing the variability or scatter of dependent variable values). A graph, which becomes a permanent part of the patient's clinical record, is of great value since it shows clearly and quickly the trends of serial measurements.

Respiratory Rate

It may seem no innovation to suggest that an accurate respiratory rate is part of a good physical examination.

Sleeping Rate

To count the rate of an anxious or crying child with a stethoscope is a waste of time. It may be that on a given clinical visit the physician will not have the opportunity to get an accurate count; if so, it is better to take none than to introduce inaccurate data into the record. The place of the parent as an observer should be recognized. A parent can be taught how to observe and record sleeping respiratory rates. Such counts, taken at the parents' bedtime, may afford invaluable data on the course of pulmonary disease (Figure 1).

Normal Limits

The data of Iliff and Lee[2] for respiratory rates are for quiet or sleeping children. The rates are expressed in means and standard deviations for both sexes with age as the independent variable (Table). For example, "normal limits" (x ± 2 SD) for respiratory rate for a 4½-year-old boy would be 23 ± 4, or from a rate of 19 to one of 27 per minute.

The early recognition of the respiratory distress syndrome in the newborn which causes increasing stiffness of the lungs, is manifest by an increased rate.[3] Recovery is thus associated with loss of stiffness and a return of the respiratory rate to normal.

Less variability (smaller standard deviations) might be observed if only sleeping respiratory rates were counted and if such rates were plotted as a function of stature, rather than age. The studies mentioned above should be extended in order to obtain information on the best independent variable (height, weight, or age), and to define values during the first year of life when the respiratory rate is dropping most rapidly from the normal newborn mean of about 47 per minute.

Barrel Chest

Pectus profundum implies a deforming of the thorax from its normal elliptical cross-sectional shape to a more circular one. The problems here in assessing thoracic deformity stem from physiological changes in both chest shape and size during the growth process. A newborn has an almost circular chest and, as the child grows, both thoracic transverse diameter (width) and anteroposterior diameter (depth) increase, but depth increases less than width and, as a result, the chest gradually assumes the more elliptical shape of the normal adult.

Thoracic Index

It is possible to measure chest depth and width with obstetrical calipers. Division of depth by width yields the thoracic index

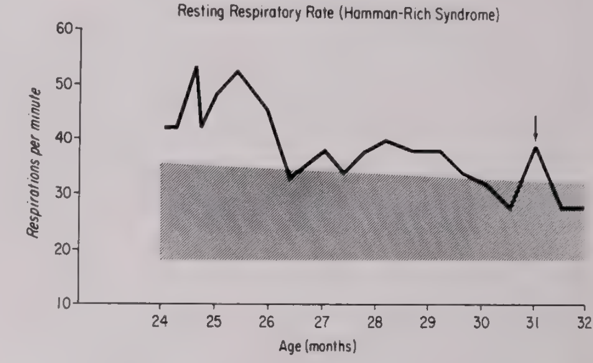

Fig. 1— Respiratory rate in a child with Hamman-Rich disease proven by open lung biopsy. Shaded area indicates normal range of respiratory rate for age. Counts were taken on serial visits to the clinic. Arrow indicates an acute respiratory infection. Corticosteroid dosage in this child was largely controlled by monitoring the respiratory rate. (Reproduced by permission of the editors, *The Bulletin of the Tulane University Medical Faculty, 27*:221, 1968.)

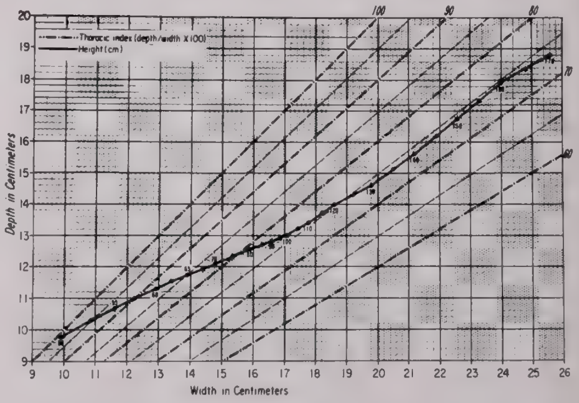

Fig. 2—Photograph of a page of the chest graphing system in use in the pediatric chest and cystic fibrosis clinics. See text. (Reproduced by permission of the editors, *The Bulletin of the Tulane University Medical Faculty*, 27:221, 1968.)

(depth-width ratio). As the thoracic index approaches unity, the chest approaches a perfect circle in cross section.

A graphing system has been developed that allows one to plot chest depth as a function of chest width and to read directly the thoracic index without the need of any further computation*. The graph also permits a physician to decide in standard deviation units how much depth, width, and thoracic index differ from expected values for children of the same sex and height (Figure 2).

As always, serial determinations are of infinitely greater value than single ones, since trends produced by the disease or by a treatment program can be assessed. Increasing deformity is a poor prognostic sign in cystic fibrosis; it also argues for a more vigorous treatment program in asthma.

Significance of Deformity

Although the necessary correlations have not as yet been made, it is a reasonable hypothesis that increasing deformity correlates with increasing functional residual capacity, that is, with the volume of air remaining in the lungs at the end of a quiet expiration. It is thus a measure of air trapping produced by chronic obstructive pulmonary disease.

With this graphing system it has been shown that children with cystic fibrosis have significantly deformed chests, primarily as a result of increases in their anteroposterior thoracic diameters. Children who subsequently die with chronic obstructive disease associated with cystic fibrosis have more severe deformities than those who continue to live, confirming the prognostic value of such measurements.

Digital Clubbing

Although clubbing of the digits has been associated with pulmonary disease since Hippocrates, its cause is still unknown. Provided congenital cyanotic heart disease can be ruled out, most digital clubbing in childhood can be related to bronchiectasis, itself a destructive process in the lung.

A method has been developed of making and measuring casts of the left index finger; the method is simple and can be learned by an office nurse for routine use. A permanent

TABLE

Normal Resting Respiratory Rate per Minute

Age (Years)	Boys Mean ± SD	Girls Mean ± SD
0- 1	31 ± 8	30 ± 6
1- 2	26 ± 4	27 ± 4
2- 3	25 ± 4	25 ± 3
3- 4	24 ± 3	24 ± 3
4- 5	23 ± 2	22 ± 2
5- 6	22 ± 2	21 ± 2
6- 7	21 ± 3	21 ± 3
7- 8	20 ± 3	20 ± 2
8- 9	20 ± 2	20 ± 2
9-10	19 ± 2	19 ± 2
10-11	19 ± 2	19 ± 2
11-12	19 ± 3	19 ± 3
12-13	19 ± 3	19 ± 2
13-14	19 ± 2	18 ± 2
14-15	18 ± 2	18 ± 3
15-16	17 ± 3	18 ± 3
16-17	17 ± 2	17 ± 3
17-18	16 ± 3	17 ± 3

Data of Iliff and Lee from both fed, sleeping and fasting, awake children. SD = one standard deviation of the mean.

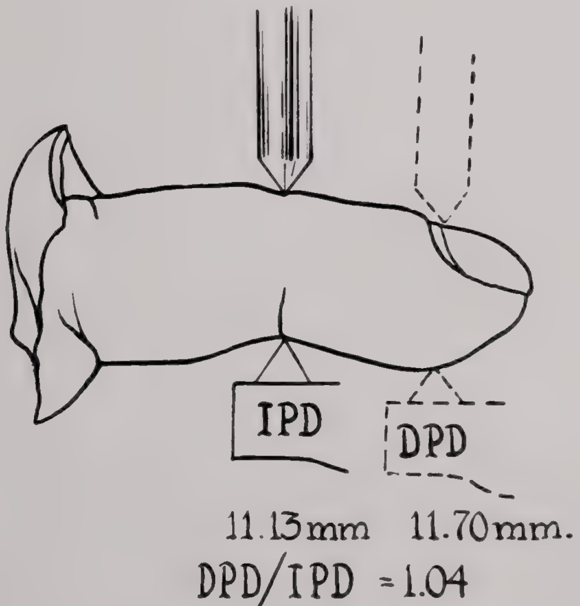

Fig. 3—Method of measuring casts of the index finger with a micrometer. Depicted cast demonstrates definite early clubbing. (Reproduced by permission of the editors, *The Bulletin of the Tulane University Medical Faculty*, 27:221, 1968).

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*These graphs have been printed by Mead Johnson Laboratories and are available without charge from the company. Each graph contains instructions for obtaining, plotting, and evaluating the two measured diameters.

record is thus obtained of the exact size and shape of the distal two phalanges of the index finger, complete even to the dermatoglyphic lines. A micrometer is used to measure the depth of the cast at the base of the nail (the distal phalangeal depth) and another depth at the distal interphalangeal fold (Figure 3). Distal phalangeal depth divided by interphalangeal depth then becomes a measure of the deformity of the terminal phalanx of the finger associated with clubbing. This ratio differentiates, better than other measurements, the fingers of children with diseases associated with clubbing from those of normal children. The ratio of the distal phalangeal depth to the interphalangeal depth is normally independent of sex, age, height, and weight from infancy into adulthood. Since the normal ratio is 0.895 with a standard deviation of .041, a value of 1.0 (equivalent to about 2½ standard deviations above the mean) has been adopted as the cut-off point between normal and abnormal values.

The practical value of these observations lies in the fact that a decision of whether a patient has clubbing or not can be made during the physical examination by a careful inspection of the lateral aspect of the *index* finger. The finger is clubbed if the depth of the finger at the base of the nail exceeds that at the terminal interphalangeal fold.

By the cast measurement system, clubbing can be quantitated and its changes with time and treatment evaluated. Serial observations of the ratio of the distal phalangeal depth to

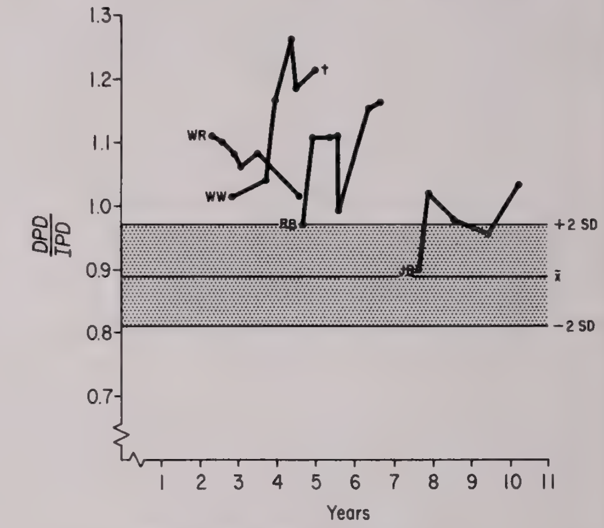

Fig. 4—Serial measurements of the ratio of the distal phalangeal depth to the distal interphalangeal fold ratio of finger casts of four boys with cystic fibrosis. Note the fluctuation in clubbing and the prognostic implications in WW whose clubbing became progressively more severe until his death (†).

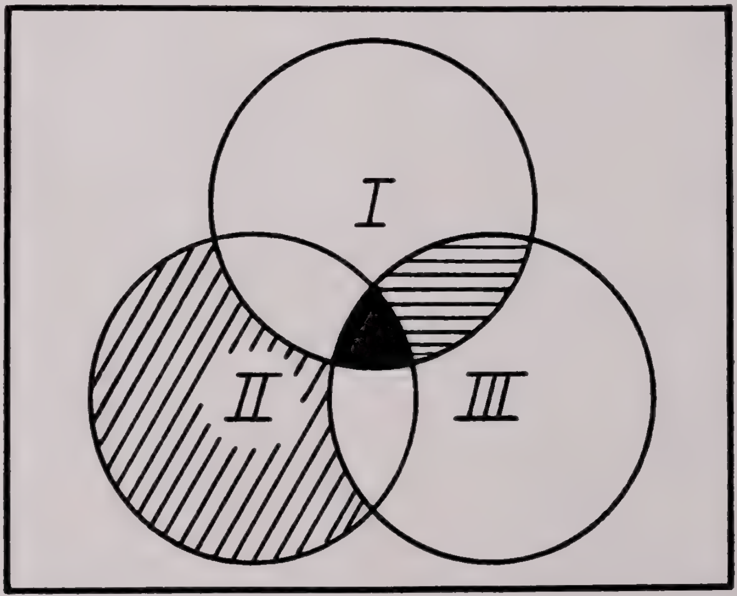

Fig. 5—A Venn diagram, showing all possible combinations of tachypnea (Set I), chest deformity (Set II), and clubbing (Set III) that can occur in a group of children with chronic pulmonary disease. (Reproduced by permission of the editors, *The Bulletin of the Tulane University Medical Faculty,* 27:221, 1968.)

the distal interphalangeal depth in children with cystic fibrosis (Figure 4), some of whom have had a dozen or more casts made over a period of several years, show curious but real increase in the severity of their clubbing.

Discussion

Since varying combinations of restriction, obstruction, and destruction occur in different types of chronic pulmonary disease, it may be possible to make a fairly accurate diagnostic guess of the basic disease by evaluating these three clinical measures. The use of a Venn diagram may clarify this point (Figure 5). In this diagram the outer rectangle encloses a group of children with chronic lung disease of at least three months' duration, as defined by obvious clinical symptoms, such as cough. All of these children will be seen by a physician because of the severity or chronicity of their disease manifestations. On physical examination a certain number will have significantly elevated respiratory rates. This "set" is separated from the children without tachypnea by placing them in a circle (Set I) within the rectangle.

It is also possible to define by significant chest deformity and significant clubbing two other groups (Sets II and III, respectively), which also are indicated by circles within the rectangle. Various combinations can be depicted by having the circles intersect. Thus, children in the center of the diagram, where all circles intersect, have tachypnea, chest deformity, and clubbing; those enclosed by the intersection of circles I and II have tachypnea and chest deformity, but do not have clubbing, and so on. Thus the Venn diagram shows all possible combinations of the three quantitated factors, including a group (outside the circles) with none of the factors but who still have chronic cough.

Experience suggests that the group of children with tachypnea, chest deformity, and clubbing (solid area, Figure 5) usually have cystic fibrosis; those with chest deformity alone have asthma (diagonal lines); and those with clubbing and tachypnea (horizontal lines) have bronchiectasis due to agammaglobulinemia or foreign body. Whether such a potential diagnostic value of the quantitative physical examination will stand rigorous prospective application remains to be tested. Pending such a test, however, one can still say that the prognostic and therapeutic implications of quantitation of clubbing and chest deformity have been reasonably established and are sufficient to justify their continued use.

Finally, this approach has great teaching value, since it helps relate pulmonary physiology, pathology, biostatistics, physical diagnosis, and therapeutics as they apply to the effects of chronic lung disease in any patient.

Summary

The "quantitative" physical examination of the lungs begins with precise measurements of (1) the resting or sleeping respiratory rate, (2) the chest depth and width, and (3) the index finger depth at the base of the nail and at the terminal interphalangeal joint.

These measurements are related to a distribution of the same measurements in normal individuals and are expressed in relation to such normal distributions (standard deviations above or below normal mean).

Tachypnea is taken as an index of restrictive lung disease, chest deformity of obstructive lung disease, and digital clubbing of "destructive" lung disease (bronchiectasis).

Such quantitation has both therapeutic and prognostic values in children with cystic fibrosis.

A Venn diagram can be used to portray logically the potential diagnostic value of this approach.

Acknowledgment

The authors are grateful to Marilyn McConnell, R.N., who routinely measures the chests and casts the index fingers of children attending the Tulane Pediatric Chest Clinic and New Orleans Cystic Fibrosis Clinic. They also thank Pamela Buchanan, B.A., who measured DPD and IPD of the finger casts.

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(Continued from Page 1428)

INTERNIST, PEDIATRICIAN, ORTHOPEDIST, GENERAL PRACTITIONER to join nineteen-man Wisconsin group located in college community of 40,000 with excellent hospital facilities. For further information contact D. R. Griffith, M.D., Midelfort Clinic, Eau Claire, Wisconsin.

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EDUCATION PLUS: What midwestern high school of 170 boys currently has alumni at Harvard, Princeton, Swarthmore, M.I.T., McGill, London and Oxford (Rhodes Scholar), welcomes Americans, and produces great hockey teams? St. Johns-Ravenscourt School, Winnipeg 19, Manitoba. Headmaster: H. John P. Schaffter, M.A. (Cambridge), 204-453-3016.

THE ADOLF GUNDERSEN MEDICAL FOUNDATION of La Crosse, Wisconsin, announces the establishment of a fully accredited three-year residency training program in Internal Medicine at Lutheran Hospital, La Crosse, Wisconsin. The hospital staff consists of a 65-man multiple specialty group with offices in a connecting modern clinic building. Eighteen fully qualified internists serve as a nucleus of the teaching program. All staff men are full-time and salaried. This clinic-hospital complex serves as a referral center for a 100-mile radius. The hospital has a 375-bed facility. An intensive in-house training program is supported by weekly guest consultants. Stipend: $600 to $700 per month, plus housing and miscellaneous. Located in a progressive community with expanding university and private college. Population 50,000. Excellent school and recreation facilities. Applications being considered at all levels. Write: Edwin L. Overholt, M.D., Director, Medical Education and Research, Gundersen Clinic, Ltd., 1836 South Avenue, La Crosse, Wisconsin 54601.

Success

To all who labor in the shadows cast by older brothers and sisters, we offer the following consolation: Elias Howe, of sewing-machine fame, was the eighth child in his family; Inventor George Westinghouse was the ninth; Novelist James Fenimore Cooper was the eleventh; Charlie Gehringer, the Detroit baseball star, was the twelfth; Naturalist Luther Burbank was the thirteenth; and the versatile Benjamin Franklin was the fifteenth.*

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The Pulmonary Function Laboratory[*]

Role in the Evaluation of Pulmonary Disease in Children

V. CHERNICK, M.D.[†]
Winnipeg, Manitoba

There can be no argument about the diagnostic value of emergency testing of pulmonary function, that is, the estimation of arterial blood gases and pH in such conditions as coma of unknown cause, cyanosis, respiratory insufficiency or acid-base disturbances. However, the pulmonary function laboratory has another role in the elective testing of children with pulmonary function disease, which is not immediately essential for the management of those particular patients.

Reasons for Assessing Pulmonary Function

Pulmonary function evaluation as an aid in differential diagnosis is most useful in the adult patient specifically in an attempt to distinguish between chronic bronchitis, emphysema and asthma. It is of little help in aiding diagnosis in children with chronic chest disease. Pulmonary function tests prior to surgery in elderly adults may be useful in predicting possible complications and help in the postoperative management. The assessment of disability such as dyspnea, impaired ability to work, etc. is useful mainly in adults and particularly for compensation cases.

In the pediatric age group the pulmonary function laboratory has its greatest usefulness in its ability to apply objective methodology to the quantitation of the degree of abnormality and in allowing the objective testing of the results of our therapy. The use of sophisticated techniques has led to a greater understanding of the pathophysiology of pulmonary diseases in infants and children.

Pathophysiology of Pulmonary Disease

In a functional classification of pulmonary diseases it is possible to define two major groups: The so-called restrictive group caused by diseases of the lung parenchyma and those affecting the chest wall, and the obstructive group which may affect upper or lower airways.

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[*] Read at the Regional Continuation Course on Chronic Respiratory Diseases in Children and Adolescents at the University of Minnesota, Minneapolis, September 17, 1968.

[†] Associate Professor of Pediatrics and Physiology, University of Manitoba. Director, Respiratory Service, Children's Hospital, Winnipeg, Manitoba.

All diseases of the chest can be fitted into this functional classification on the basis of their principal functional abnormality. However, some diseases, for example cystic fibrosis, may have features of both an obstructive airway disease and a parenchymal disease, particularly when lung tissue is destroyed.

All of these diseases appear to result in similar physiologic abnormalities, that is, they lead to a mis-matching of ventilation and perfusion in the lung, which is one of the commonest causes of hypoxemia. There is an increase in the work of breathing which increases both the metabolic demand for oxygen and the amount of CO_2 produced which subsequently must be eliminated by the lungs. When severe, a particular process may lead to a decrease in alveolar ventilation with consequent CO_2 retention, respiratory acidosis and hypoxemia.

There are conditions outside of the chest cage which may adversely affect alveolar ventilation and produce abnormalities of the blood gases, for example, barbiturate intoxication or anesthesia. The resultant effect of these abnormalities of pulmonary function is hypercapnia, hypoxemia and acidemia. The acidemia may be both a respiratory and a metabolic acidosis. In order to functionally classify a particular disease that a patient presents with, a history, physical examination and radiologic examination are extremely important. In addition, it is possible by using simple pulmonary function tests to delineate between restrictive and obstructive disease and to quantitate the degree of abnormality.

Restrictive Disease

Disease of the lung parenchyma may be associated with a decrease in lung volume, as in pneumonia, atelectasis or bronchiectasis, or by a decreased distensibility of the lung, such as in hyaline membrane disease or pulmonary fibrosis. Examples of diseases which may affect the chest wall are kyphoscoliosis, phrenic nerve palsy and polio.

By simple spirometry one can measure the vital capacity (the sum of the respiratory reserve volume and the expiratory reserve volume); in restrictive disease it is found to be reduced. For example, following a lobectomy where 25 per cent of the lung has been removed, all lung volumes, including residual volume or the functional residual capacity, appear to be reduced and are reduced to the same extent. There is no impairment in the ability to forcibly expire most of the vital capacity within one second following a maximal inspiration.

Obstructive Disease

Obstructive diseases of the airways may affect upper airways, such as in choanal atresia* or foreign body aspiration, or lower airways, such as in asthma.

In contrast, the patient with obstructive disease such as asthma has a reduced vital capacity primarily on the basis of an increase in the functional residual capacity. There is a marked reduction in the volume of air which can be forcibly expired after one second following a maximal inspiration because of obstruction to air flow. The measurement of vital capacity and timed vital capacity, that is, the percentage of the vital capacity that can be forcibly expired in one second, is one of the simplest and most informative tests that can be done. It does not take expensive or sophisticated equipment and can be accomplished in a few minutes. However, with the use of more complicated measurements it has been possible to achieve a greater understanding of the pathophysiology of a number of disease processes.

Asthma

Asthma is associated with an increase in the allergic reactivity of the bronchial smooth muscle, and there may or may not be a superimposed respiratory infection during the acute attack. The allergic hyperreactivity results in bronchospasm, edema of the bronchiolar epithelium and accumulation of viscid mucus, resulting in expiratory airway obstruction, ventilation-perfusion abnormalities and, in severe cases, areas of atelectasis because of mucous plugs. The expiratory airway obstruction leads to a marked increase in the work of breathing; the patient has an increased functional residual capacity and residual volume accounting for the increase in the anteroposterior diameter of the chest. Obstruction of airways is associated with an increased frequency of pneumothorax in such patients. The increased work of breathing, when marked, leads to alveolar hypoventilation with resultant hypercapnia and hypoxemia. Hypoxemia is also caused by the ventilation-perfusion abnormalities and because of blood flow through areas of lung which are not ventilated. An insufficient supply of oxygen for aerobic metabolism is associated with a pyruvic and lactic acidemia and hence a metabolic acidosis.

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*See Test Your Word Score page 1401.

The respiratory acidosis is associated with clinical symptoms of restlessness, fatigue, and anxiety, and when very severe leads to delirium and stupor. The end result in very severe cases of asthma is shock and cardiac arrest. With this pathogenetic scheme in mind, therefore, we can direct our therapeutic approach to decreasing bronchospasm, decreasing the viscosity of mucus, providing oxygen and treating respiratory failure when it supervenes.

Cystic Fibrosis

Evaluation of the mechanical properties of the chest in a patient with moderately-severe cystic fibrosis reveals an increase in the rate of respiration and in the minute ventilation. A large proportion of this minute ventilation is wasted or dead-space ventilation so that, despite the increased work of breathing, a great deal of the effort is wasted. The vital capacity is decreased as is the one-second vital capacity, denoting airway obstruction. The compliance of the lungs is decreased so that it is more difficult to move air in and out; the vital capacity is decreased because of an increase in the residual volume, and this can be noted clinically in the expanded anteroposterior diameter of the chest wall. Direct measurements of airway resistance confirm the increase of resistance.

How well are blood and gas matched within the lung? Washing nitrogen out of the lung by breathing 100 per cent oxygen is inefficient in these patients, showing that there is maldistribution of ventilation, that is, large portions of the lung which are very poorly ventilated. I have already mentioned that the dead-space ventilation is increased. These patients have large arterial-alveolar nitrogen gradients, a test which is used to denote how well alveoli are matched in terms of ventilation and perfusion. An increase in the a-A nitrogen gradient demonstrates poor matching of blood and gas primarily caused by alveoli which are under-ventilated and relatively overperfused with blood.

This type of alteration leads to hypoxemia. There are areas that receive a blood supply and are completely unventilated since, in the very severe case, the arterial pO_2 does not go over 500 mm. Hg. even when the patient is breathing 100 per cent oxygen. That is, there are true right to left shunts within the lung in very severe or terminal cystic fibrosis patients. The end result of these abnormalities on the arterial blood in the moderately-severe case is an elevated pCO_2; if this is an acute case the pH may be decreased, but if there has been time for renal compensation the pH may be close to normal. The bicarbonate concentration may be normal or even increased, depending on renal compensation. The arterial pO_2 while breathing room air is decreased and, if severe enough, is associated with cyanosis. As I have mentioned, the PO_2 while breathing 100 per cent oxygen may be normal or decreased.

The frequent measurement of pulmonary function has been found to be of great help in cystic fibrosis patients, since it has been possible to predict incipient respiratory failure before there has been much clinical change. In other words, these tests, particularly the vital capacity and the measurements of the residual volume or functional residual capacity, have enabled us to see progression of the disease process and warn us that acute respiratory failure may occur. In these patients it has been possible to institute a vigorous therapeutic regime in an attempt to avoid the complication of respiratory failure.

Arterial Blood Gases

As I have indicated, one of the simplest, most inexpensive and useful tests of pulmonary function is the measurement of the vital capacity and one-second vital capacity. This measures many of the mechanical properties of the lungs but does not indicate how effectively our ventilatory efforts are in oxygenating the blood and removing carbon dioxide. Since the level of carbon dioxide in the blood is inversely proportional to the alveolar ventilation, the estimation of arterial PCO_2 is now commonly done in most hospitals. Probably the most widely used in children is the Astrup technique which requires only a couple of capillary tubes full of arterialized capillary blood for the estimation of arterial PCO_2 and pH, and an estimate of the metabolic component of the Henderson-Hasselbalch equation, the bicarbonate concentration. Not only does the estimation of the arterial PCO_2 tell us about the status of the alveolar ventilation in a particular patient, but it can also help us in estimating the alveolar oxygen tension which must be present.

The three component gases in the alveolar air are nitrogen, oxygen and carbon dioxide. Since nitrogen is inert, that is, not consumed, there is an inverse relationship between the partial pressure of carbon dioxide in the alveolar gas and the partial pressure of oxygen. The total of the two gas tensions must always, at sea level, be equal to approximately 150 mm. Hg. Thus, during normal alveolar ventilation when the arterial PCO_2 is approximately 40, the alveolar oxygen tension is approximately 110 mm. Hg. When alveolar ventilation is reduced, the arterial PCO_2 rises and the alveolar oxygen concentration must fall.

Knowing the alveolar concentration, however, one cannot predict with certainty the arterial oxygen concentration because right-to-left shunts, diffusion abnormalities, and ventilation-perfusion imbalance may all contribute to a gradient between the alveolar and arterial concentrations. Thus, to be absolutely certain, one must directly measure the arterial oxygen tension. However, one can say that the arterial PO_2 can be no higher than the estimated alveolar oxygen concentration. I must point out that these relationships are true only when the patient is breathing room air. When he is breathing 100 per cent oxygen the nitrogen concentration in the alveolar air is reduced and replaced by oxygen.

Summary

The pulmonary function laboratory has helped in our understanding in the pathogenesis of chronic childhood respiratory diseases and is used to evaluate the degree of functional abnormality and to assess our attempts at therapy. It is not possible, however, for all physicians to have access to large, expensively-equipped, sophisticated pulmonary function laboratories, but a great deal of information on a particular patient can be obtained by simple spirometry and by techniques for estimating the arterial PCO_2. Also, by the use of sophisticated techniques, it may be possible to predict and avoid respiratory failure in some of the chronic diseases of childhood.

The future course of the pulmonary function laboratory is predictably bright. Although there has been a tendency in the past to consider the lung as a simple elastic balloon, there is now a considerable body of evidence which indicates that the lung is a very active metabolic organ: the central clearance organ for many of the body's internal secretions, such as bradykinin, prostoglandins and other substances. In the future, respiratory physiologists will increasingly be considering the lung as an active metabolic organ, and it is by this sort of approach that our knowledge of the chronic respiratory diseases of childhood will be greatly advanced.

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A good dinner, and company that pleases me mightily.—Samuel Pepys.

X-Ray Diagnosis in the Child[*]

JUSTIN WOLFSON, M.D.[†]
Minneapolis, Minnesota

THE X-RAY BEAM, as it transverses the chest, distinguishes four types of structure: calcium (bone), soft tissue (e.g., muscle, heart, fluid), fat (subcutaneous), and air (lung). The variable distribution of these densities on a plain film provides the means for radiographic diagnosis.

Because children grow, the roentgenogram of the chest progressively changes; however, a range of normal for varying age levels is recognized. Familiarity with the normal and its variations is requisite, for it permits recognition of the abnormal.

Steps in Diagnosis

Abnormal infiltrations of the lung may be produced by a bewilderingly large number of conditions. In order that these may be distinguished and a diagnosis achieved, the following steps are necessary:

Description

The lesion or lesions must be carefully and accurately described (location, size, contour, sharpness, multiplicity, calcification, associated disease, et cetera).

Correlation

The appearance of the lesion must be correlated with other factors: age of the patient, acuteness or chronicity ("timing"), alveolar or interstitial pattern, benign vs. malignant features and infectious character of the lesion. This process, if accurate, permits rapid exclusion of improbable diagnostic possibilities and the development of useful differential diagnoses.

The radiographic observations must be correlated with pertinent history, physical findings, and laboratory data.

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[*] Presented at the Regional Continuation Course on Chronic Respiratory Diseases in Children and Adolescents at the University of Minnesota, Minneapolis, September 17, 1968.

[†] Department of Radiology, University of Minnesota, Minneapolis, Minnesota.

Methods have been devised which, in an efficient and reproducible manner, attempt to exclude undesirable diagnoses and to provide ultimately an accurate diagnosis (see Table).

Chest Films

The chest film of the newborn may appear different on inspiration and expiration; the thymus gland is large, and artefacts, such as skin folds, can readily mislead the unwary. Certain diseases are characteristic of the newborn period: hyaline membrane disease, aspiration pneumonia, and diaphragmatic hernia.

Mediastinal Masses

It is convenient and useful to allocate mediastinal masses to one of three compartments: anterior, middle, or posterior. The contour, symmetry, presence or absence of calcification, and possible other associated findings, such as pleural fluid, should be observed. Benign thymoma, lymphosarcoma, teratoma, and primary tuberculous complex are well-known examples.

Increased Chest Volume

The volume of a hemithorax may be in-

TABLE

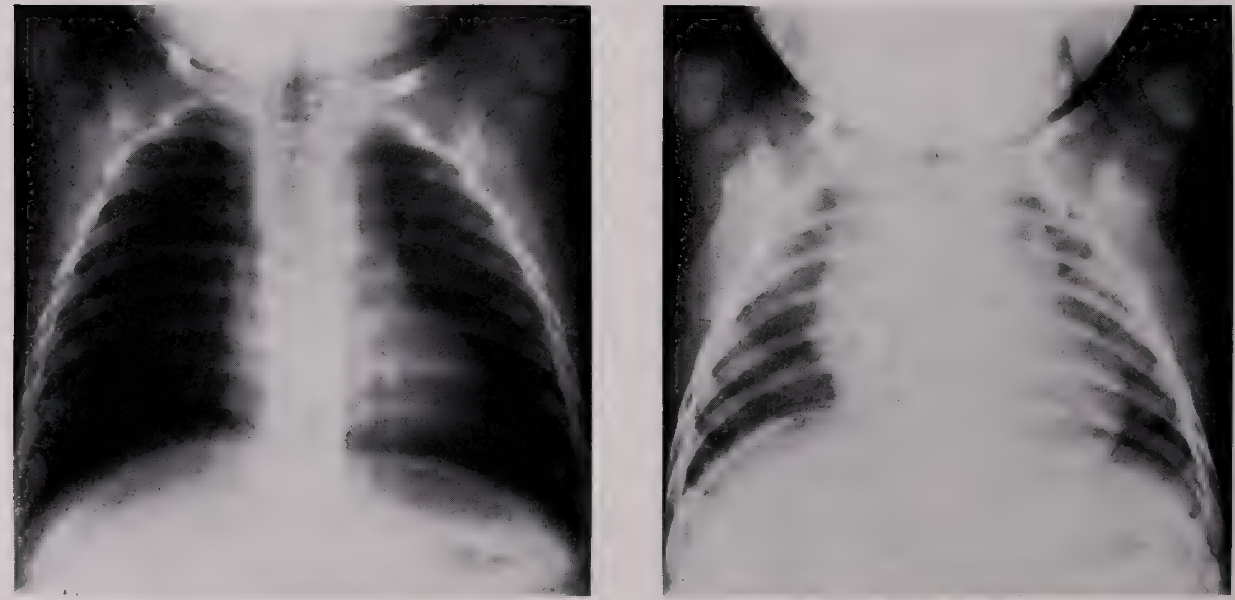
Classifications of Pulmonary Disease

I. AGE OF CHILD
  A. Newborn
  B. Later

II. LOCATION
  A. Mediastinum: anterior, middle, posterior
  B. Lungs
    1. Local, multiple, generalized
    2. Alveolar as interstitial
    3. Increased or decreased volume
  C. Pleura
  D. Diaphragms

III. ORIGIN OF DISEASE AFFECTING LUNG
  A. Local
    1. Pneumonia-bacterial
    2. Tuberculosis
  B. Systemic disease
    1. Nephrosis
    2. Rheumatoid arthritis
    3. Cystic fibrosis of the pancreas
    4. Chronic granulomatous disease (C.G.D.)
    5. Leukemia
  C. Localized disease in body affecting lungs
    1. Metastatic tumor
    2. Metastatic abscess
    3. Extension of disease (liver abscess → lung)
    4. Pulmonary infarct

IV. OTHER SUBDIVISIONS
  A. Infectious vs. neoplastic
  B. Acute vs. chronic
  C. Genetically transmitted or congenital vs. acquired



Figs. 1 and 2—Normal chest of an infant, inspiration and expiration films. On inspiration the right diaphragm lies at the level of the ninth to tenth posterior rib. On expiration the diaphragm lies at the level of the eighth posterior rib. With expiration the lung fields are hazy and the mediastinum is widened. This widening is due to the thymus gland, which may assume variable contours. On the right, at the level of the seventh posterior rib (Figure 2) the lower margin of the thymus forms a notch where it meets the true cardiac margin.

creased by (1) an increase in size of the lung from emphysema, (2) a growing mass within the lung or pleural space, (3) an extensive pleural effusion, with or without mass, and (4) tension pneumothorax.

Extrinsic compression upon or a foreign body within a bronchus may produce emphysema, not infrequently followed by atelectasis and even bronchiectasis. A lobe may continue to enlarge, producing compressive atelectasis of adjacent lobes and a shift of mediastinal structures such as in idiopathic lobar emphysema. Masses may extend the lung field from the mediastinum, chest wall, or diaphragm, or may lie free of these structures within the lungs.

Diminished Chest Volume

Chronic disease, such as may be associated with tuberculosis or lobectomy and pneumonectomy, or primary hypoplasia of the lung, may result in diminished volume. Each has features which are of aid in producing a specific diagnosis.

The Diaphragm

Masses may project through or originate from the diaphragm. The diaphragm may be eventrated on one or both sides or may appear to be eventrated when it is not, such as with diaphragmatic herniation or with collection of fluid between the lung and diaphragm (infrapulmonary effusion).

Interstitial Disease

Numerous disease entities affect the interstitial structures of the lung. Thus thickening of peribronchial and perivascular structures, of interlobular septate, and finally of alveolar walls occurs. Pure interstitial disease is distinctive in appearance. Since the process is subacute or chronic, an interstitial pattern serves as a timing device as well, and its presence allows us to exclude most alveolar (acute) processes.

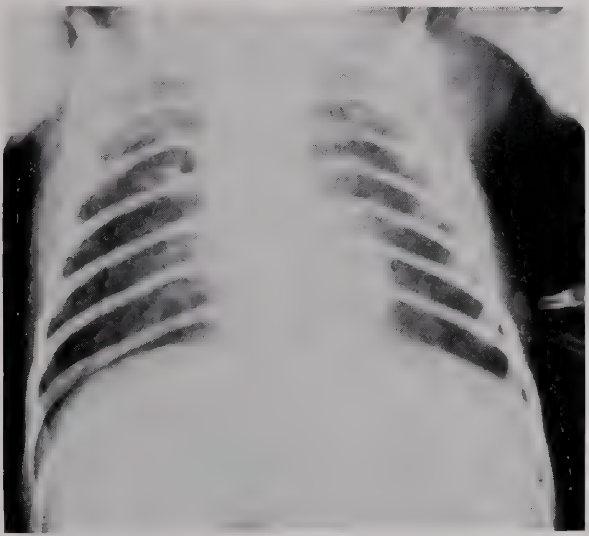
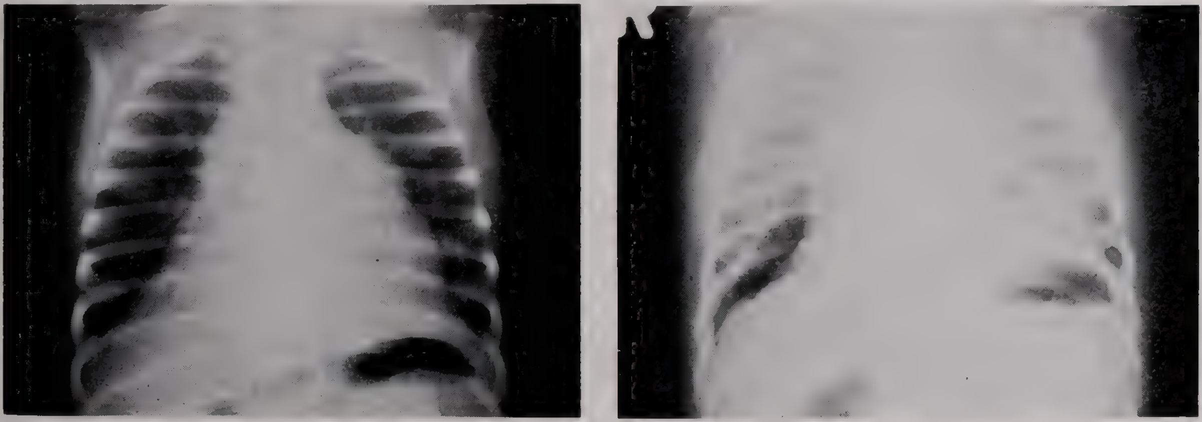


Fig. 3—Normal chest with vertical skin folds overlying right hemithorax. This appearance is produced by the juxtaposition of room air with a fold of skin while the infant lies supine upon the x-ray table. In this instance there are three such folds. The importance of such a fold is that it may simulate a pneumothorax, as does the most lateral of the three folds in this patient.



Figs. 4 and 5—Marked bilateral eventration of the diaphragms simulating cardiac or pulmonary disease. A normal cardiac silhouette overlies almost vertically oriented, sharply defined diaphragmatic leaves. In Figure 5 the full thickness of the diaphragms can be appreciated because air has been introduced into the peritoneal space. Actually a careful evaluation of contours and lung fields in Figure 5 alone permits one to exclude cardiac and pulmonary abnormality. However, as in this case, an eventrated diaphragm on one or both sides may produce diagnostic problems. Eventration, even as prominent as in this patient, rarely causes clinical symptoms. A sibling of this child also had bilateral eventration of the diaphragms.

Multiple Large Parenchymal Lesions

Multiple, large, spherical masses are usually interstitial and due to metastatic tumor, such as Wilms's. Multiple, rapidly enlarging, poorly defined masses, with or without excavation, suggest abscess formation.

Spherical radiolucencies, especially within an infiltrate, may be a tipoff to the presence of a staphylococcal pneumonia with pneumatocele. Occasionally, cavitation of a cyst or an abscess within a lobe of lung may be different to distinguish from a loculated hydro or pyopneumothorax. In such instances the absence of inflammatory changes in the remainder of the hemithorax tends to rule out an empyema.

Alveolar Disease

Normally the alveoli are air-containing. Any disease which permits the air within contiguous alveoli to be replaced by fluid of any sort will produce a characteristic opacification, which may be lobular, segmental, or lobar. Examples of extensive alveolar processes are lobar pneumonia, pulmonary edema, pneumocystis carinii, and pulmonary infarction.

There is nothing about the opacification which is distinctive except that it is alveolar. However, the distribution of the opacification and possible associated abnormalities usually lead to the correct diagnosis.

Alveolar disease may be spherical, but, unlike interstitial disease, it tends to be rapidly changing and therefore confluent. Thus, fat embolization with hemorrhage, chicken-pox pneumonia, and transfusion reaction may give this appearance.

Alveolar and interstitial processes may coexist and be difficult to distinguish from one another. Sequential films may be necessary for adequate interpretation. An example of a disease which often has a recognizable, interstitial component (due to chronic inflammation) and alveolar component (characteristically recurrent) is idiopathic hemosiderosis.

Conclusions

Radiographic patterns of pulmonary disease are a reflection of underlying pathologic processes, both gross and microscopic, and are useful in making diagnoses. However, they are not infallible. Equally important are the availability to the radiologist of pertinent clinical data and the opportunity for radiologist and pediatrician to peruse films together.

Biologic Peril

Abundance and affluence have brought new dangers of overweight, musculoskeletal problems from sedentary living, and skin disorders from sun bathing. Sociomedical prophets warn that man ignores his basic biological nature at his peril. The patient meanwhile protests the high cost of high quality medicine, sometimes looks on his physician more as a technician than an adviser, and demands powerful drugs for even his minor ills. At the same time complaints have been heard that the physician-patient relationship is becoming dehumanized; longings are aften expressed for the fatherly family physician of the past. As populations increase and medicine develops ever-greater technical refinements, a still more automated version of medical care, with punch-card case histories and diagnosis by computers hovers over the patient.*

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*The Patient's Progress, Edited by Felix Marti-Ibanez, 1962.

Editor's Note: It's nice to know that someone else thinks like we do.

Specialization

No specialist has yet advanced the thesis that the part is greater than the whole, but all of them believe in their hearts that their own part is equal to the whole.*

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*Ogilvie, H., in Richard Macgraw: Ferment in Medicine, 1966.

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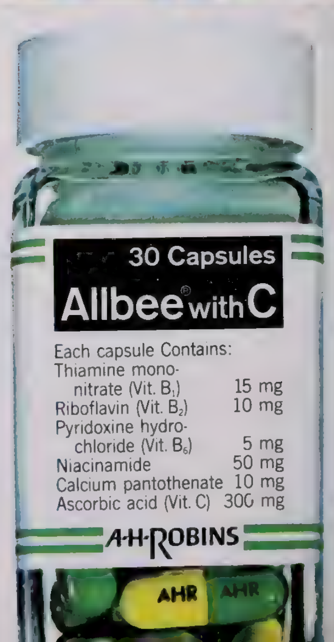
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Pulmonary Function Evaluation with ^{133}Xenon*

JOSE R. MEDINA, M.D.†
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MERLE K. LOKEN, M.D., Ph.D.†
Minneapolis, Minnesota

THE IMPORTANCE of studying the relationships between pulmonary blood flow (perfusion) and pulmonary ventilation has been widely recognized. A variety of pathological disorders involving the pulmonary circulation or the broncho-alveolar structures produce changes in ventilation and perfusion which result in abnormal arterial blood gases. Since the pathology may be localized or diffuse, and since some disorders are amenable to surgery, it becomes increasingly important to identify their exact extent and location, and to determine the functional status of the remaining lung.

Bronchospirometry‡ and radioisotopic techniques have been used in regional evaluation of pulmonary function. Bronchospirometry, however, requires endotracheal intubation which limits its use; the simplicity of radioisotopic techniques makes regional evaluation of pulmonary function a practical clinical procedure. Various radioactive aerosols have been administered by inhalation and followed by scanning to study ventilation in the various areas of the lungs.[1,2] The techniques of lung scanning after the injection of macroaggregates of albumin tagged with ^{131}I or ^{99m}Tc have been used extensively in the study of the pulmonary circulation and in the diagnosis and follow-up of pulmonary embolization.[3,4] With the introduction of the radioactive gases xenon, krypton, and oxygen, the study of regional ventilation has become feasible;[5,6] this allows differentiation of diseases that affect the pulmonary vasculature alone, i.e., pulmonary embolism, from those that affect both perfusion and ventilation, such as pulmonary emphysema.

Materials and Methods

In 1955 Knipping and co-workers introduced ^{133}xenon for the study of ventilation and perfusion.[7] ^{133}Xenon is a chemically inert gas

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*Read at the Regional Continuation Course of Chronic Respiratory Diseases in Children and Adolescents at the University of Minnesota, Minneapolis, September 17, 1968.

Supported by grants from the National Academy of Sciences (Picker Foundation), the Graduate School, University of Minnesota and the Minnesota Respiratory and Health Association.

†Departments of Medicine and Radiology, University of Minnesota.

‡See Test Your Word Score page 1401.

with a physical half-life of 5.27 days. Because of its solubility characteristics, it diffuses readily from the pulmonary blood into the alveolar air and is rapidly eliminated by the respiration. If the patient holds his breath after an intravenous injection of ^{133}xenon, redistribution of xenon does not occur and the pattern of radioactivity detectable by external monitors corresponds to the distribution of pulmonary blood flow. Ventilation is studied by inhalation of xenon gas from a closed circuit spirometer; the distribution of radioactivity indicates regional ventilation. The rate of clearance (washout) of the injected xenon from the lung is also a function of ventilation.

Diverse methods for quantitative analysis of ventilation and perfusion have been designed.[6,8] These methods compare the fractional counts recorded during the uptake and clearance of radioactivity by scintillation probes placed externally over the chest wall. With the Anger scintillation camera the distribution of ventilation and perfusion is displayed on scintiphotographs.[9] The gamma rays emitted from ^{133}xenon, administered by injection or inhalation, are displayed as flashes of light on an oscilloscope which is photographed with a polaroid camera. Sequential scintiphotographs are obtained during the uptake and clearance of xenon. Strip chart recordings are obtained of the uptake and clearance of radioactivity as displayed in each quadrant of the scintillation crystal. In addition, we have now installed interface equipment so that the data are recorded on magnetic tape for computer analysis. The computer program is written in a manner which permits an evaluation of ventilation and perfusion to be made on a regional basis.

Basic Patterns

Intravenous Xenon

Figure 1 shows the curves obtained with intravenous injection of 4 mc of ^{133}xenon. The upper tracing records the respiration, the lower a strip chart recording. The patient inspires slowly up to the point of maximal inspiratory capacity and holds his breath. A rise and plateau of radioactivity is recorded, corresponding to the xenon in the pulmonary circulation. The scintiphotographs obtained at this time show the perfusion to various areas of the lung. Once the patient resumes breathing, xenon clears from the lung as seen by fall-off of the radioactivity. The curve of xenon clearance is called the washout curve.

Inhalation of Xenon

Figure 2 shows a curve obtained from a strip chart recording after inhalation of xenon. The ^{133}xenon gas has been added to a closed circuit spirometer from which the patient takes a single deep breath up to his maximum inspiratory capacity and holds it while a plateau of radioactivity is recorded. He then resumes breathing of xenon gas in air which allows a uniform distribution of xenon throughout the lung. After "equilibration," a second plateau is recorded by again asking the patient to take

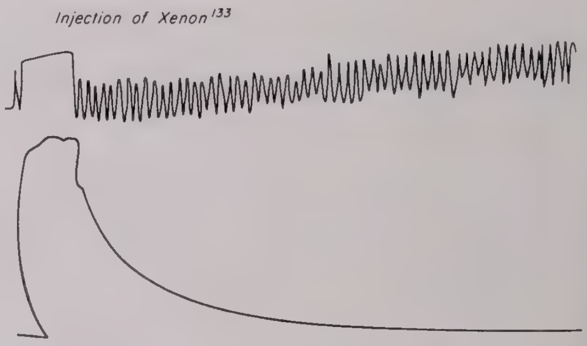

Fig. 1—Upper tracing records the spirogram; the lower, the uptake and clearance of ^{133}xenon injected intravenously. Notice that during breathholding a plateau is inscribed in the lower tracing. The distribution of radioactivity during this plateau indicates perfusion.

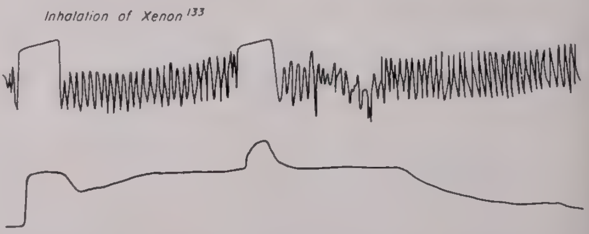

Fig. 2—Upper tracing records the spirogram; the lower, the uptake of ^{133}xenon during the inhalation of the radioactive gas from a spirometer. The first plateau corresponds to the distribution of ^{133}xenon after a single breath. A rebreathing period follows this initial breathholding to allow equilibration of the gas throughout the system. The second peak represents breathholding after equilibration and is used for correction of geometry and lung volume.

a deep breath to his maximum inspiratory capacity and to breathhold. The data obtained from this plateau is used for correction of lung volume and geometry.[6] Once a new base line is recorded the rebreathing of xenon is terminated and washout curves are recorded.

Results

In normal subjects studied in the upright position, the apices accumulate less radioactivity than the bases due to the effect of gravity on the distribution of blood flow.[10] The distribution of ventilation is more uniform, although there is proportionately less ventilation in the apices than at the bases. The clearance of xenon is also uniform. From the washout curves the rate of clearance can be measured; half of peak radioactivity after injection (T $\frac{1}{2}$) is cleared in 25 to 30 seconds.

Pathologically three patterns of abnormality of the distribution of blood flow and ventilation have been described: (a) abnormal perfusion with normal ventilation; (b) abnormal ventilation with normal perfusion; and (c) abnormal ventilation and abnormal perfusion. Individual patients may show various combinations of abnormalities. The following cases illustrate some of these changes.

Obstruction of Right Pulmonary Artery

Figure 3(b) shows the scintiphotographs obtained on a patient with obstruction of the right pulmonary artery. There are no scintillation events in the right lung. The ventilation photographs show that ventilation on the right side is preserved to some extent despite the absence of pulmonary blood flow. Some cases of pulmonary embolism also demonstrate preserved ventilation despite absent perfusion.

Bronchial Asthma

Patients with bronchial asthma have impaired ventilation with adequate perfusion,[11] and thus may present clinically with a low pO_2.

Most frequently poor ventilation and poor perfusion coexist, as seen in Figure 4. Notice that in the photographs the areas of poor perfusion initially show as dark areas and that

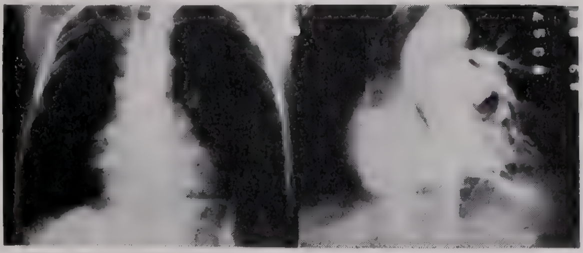

Fig. 3(a)—Chest x-ray and right ventriculogram in a patient with tetralogy of Fallot. The contrast material is seen simultaneously in the aorta and pulmonary artery because of right to left shunt through the ventricular septal defect. Notice that no contrast is seen in the right lung, indicating obstructed flow due to occlusion of the right pulmonary artery.

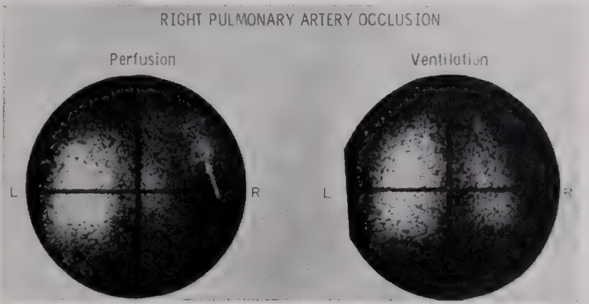

Fig. 3(b)—Perfusion-ventilation studies with ^{133}xenon of the patient in Fig. 3a. In the perfusion photograph there is a considerable decrease of radioactivity in the right lung (the reader's right) when compared with the left lung. The arrow points to radioactivity in the right arm. The ventilation photograph demonstrates relative preservation of ventilation in the right lung.

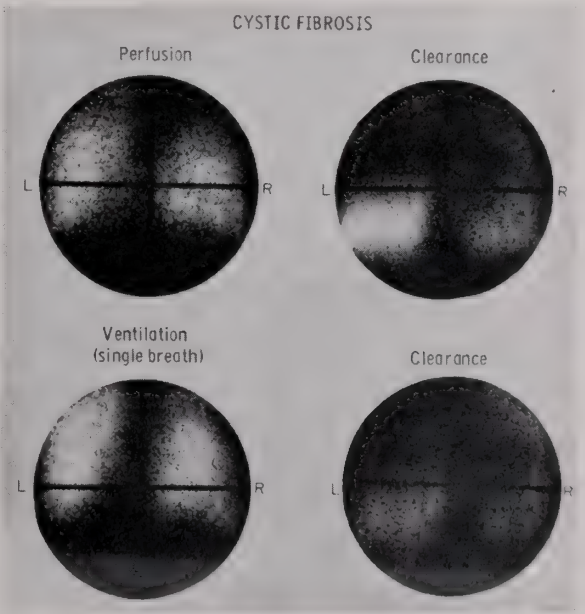

Fig. 4—Scintiphotograms of a 13-year-old boy with cystic fibrosis. The distribution of perfusion and ventilation is irregular with marked decrease in the left lower and right upper quadrants. Retention of radioactivity in the lower quadrants during the clearance phase indicates poor ventilation of these areas.

during clearance the same area is seen as a bright spot. This is due to retained radioactivity in poorly ventilated lung while the remainder of the lung has cleared.

A single intravenous injection of xenon permits study of perfusion (plateau) and ventilation (washout). In cases where inhalation is not possible the injection alone could detect areas of abnormal perfusion/ventilation as shown in Figures 5(a) and (b). The chest x-ray shows an area of hyperlucency with decreased bronchovascular markings, consistent with an emphysematous bulla. The injection of xenon demonstrates poor perfusion to this area, and the photographs during washout show the same area retaining radioactivity indicating poor ventilation as well.

Comments

Clinical Application

A practical application of regional ventilation and perfusion studies is the preoperative evaluation of patients where resectional lung surgery is contemplated. Figure 6 shows a patient with recurrent respiratory infections and bronchiectasis with roentgenographic evidence of destruction of the right upper lobe and changes in the left lower lobe which are not as well defined. The scintiphotographs show bilateral disease with poorly ventilated and poorly perfused areas in the left lower lobe as well as in the right upper lobe.

Insignificant Radiation

The radiation exposure in these procedures is low when compared with standard radiological techniques. The highest gonadal dose after the intravenous injection of 5 mc of ^{133}xenon has been reported to be 1 millirad,[12] which corresponds to the radiation dose from unavoidable cosmic radiation during about three days of life (at sea level). For the ventilation study with rebreathing, the calculated exposure is 35 millirads per minute, which is low compared with 3000 millirads per minute for fluoroscopic studies.

Summary

The technique of pulmonary function eval-

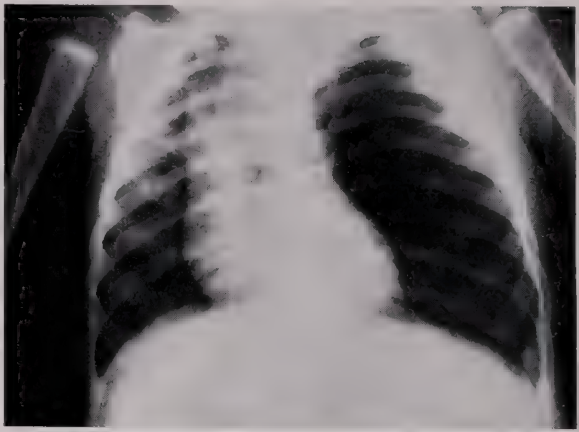

Fig. 5(a)—Chest x ray of a six-month-old patient. Notice the lack of bronchovascular markings in the left upper lobe and the mediastinal shift to the right.

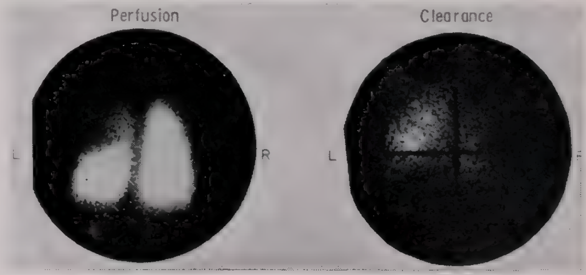

Fig. 5(b)—Scintiphotographs of patient whose chest x-ray is shown in Fig. 5a. The left upper lobe (the reader's left) shows decreased perfusion. The photograph taken during the clearance phase after the injection of ^{133}xenon shows radioactivity retained in the left upper lobe indicating poor ventilation.

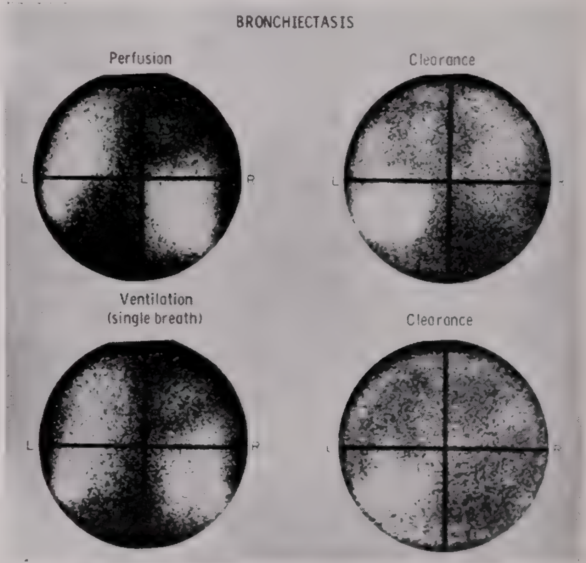

Fig. 6—Scintiphotographs of a patient with bronchiectasis in the right upper lobe and left lower lobe. Notice the lack of uptake in right upper (reader's right) and left lower (reader's left) quadrants in both the perfusion and ventilation photographs. The scintiphotographs obtained during the clearance of xenon show marked retention of radioactivity in the same areas.

uation with ^{133}xenon has been reviewed, and cases have been presented to illustrate some of the clinical applications. The advantages of the Anger scintillation camera have been described. It permits visual display of physiological phenomena, and topographic localization of functional abnormalities.

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Bad Health and Big Shots

The specialists inform me that almost everybody had syphilis in the sixteenth century, including Henry the Eighth, who also endured chronic, malignant wife-trouble. Charles V, Holy Roman Emperor of the German people, was strong, cautious, brave and wise, but he ate too much. If he had had a passion for Wheaties instead of roast pig the destinies of Europe might have been quite different. Samuel Pepys, whose lady-killing tendencies are now blamed on a scar in his perineum, was presumably saddled with gall stones (many eighteenth-century surgeons carried handfuls of gravel around in their pockets for display purposes if an operation failed to produce stones).

Edward Gibbon had an embarrassing what-is-it dangling round his knees, unwieldy as his Roman Empire. Martin Luther struggled along for sixty-two years with nerve trouble, ear trouble, blood trouble, and heart trouble. Henry Fielding thumbed his nose at gout and dropsy and wrote "Tom Jones" and "Amelia." Alexander Pope had spells when he couldn't stand unless laced in a frame. He averred that, at a distance, he looked like a small windmill. The mere mention of Thomas De Quincey's ailments makes hardened medicos grow pale, and yet this strange genius kept plugging for seventy-five years.*

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*Sprague, Marshall: The Business of Getting Well, 1943.

A hole is nothing at all, but you can break your neck in it.—Austin O'Malley

Minnesota State Board of Medical Examiners

Notice is hereby given that a public hearing will be held pursuant to Minnesota Statutes, Section 15.0412, Subdivision 4, in the above entitled matter, in the office of Minnesota State Board of Medical Examiners, 496 Lowry Medical Arts Building, Saint Paul, Minnesota, on November 8, 1969, commencing at 10:30 a.m. and continuing until all representatives of associations or other interested groups or persons have had an opportunity to be heard concerning adoption of the proposed amendments to the rules captioned above by submitting either oral or written data, statements, or arguments. Statements or briefs may be submitted without appearing at the hearing.

A copy of the proposed amendments to rules is listed below:

Minnesota State Board of Medical Examiners
By J. P. Medelman, M.D.
Secretary-Treasurer

I. Proposed amendment to Rule ME 2(b)(1).

Rule ME 2(b)(1) is hereby amended by striking and deleting the whole thereof and by substituting the following in lieu and in place thereof:

"(1) If the applicant is a graduate of a medical or osteopathic college approved by the Board, original or certified copy of diploma from such medical or osteopathic college, as the case may be, indicating that the applicant has satisfactorily completed a course of study acceptable to the Board and that he has received from such college the degree of Doctor of Medicine or Doctor of Osteopathy."

II. Proposed amendment to Rule ME 2(b)(2).

Rule ME 2(b)(2) is hereby amended by striking and deleting the whole thereof and by substituting the following in lieu and in place thereof:

"(2) If the applicant is currently enrolled in the final year of study at an approved medical or osteopathic college, a transcript of his credits, together with evidence, satisfactory to the Board, that the applicant has satisfactorily completed the course of study prior to such final year at an approved medical or osteopathic college. Prior to admission to the licensing examination, the applicant shall file with the Board the original or a certified copy of a diploma from a medical or osteopathic college approved by the Board indicating that the applicant has satisfactorily completed a course of study acceptable to the Board and that he has received from such college the degree of Doctor of Medicine or Doctor of Osteopathy."

III. Proposed amendment to Rule ME 2(c).

Rule ME 2(c) is hereby amended by striking and deleting therefrom the words "Bachelor of Medicine, Bachelor of Medicine and Surgery".

IV. Proposed amendment to Rule ME 4(b)(2).

Rule ME 4(b)(2) is hereby amended by striking and deleting therefrom the words "Bachelor of Medicine, Bachelor of Medicine and Surgery".

V. Proposed amendment to Rule ME 11(g).

Rule ME 11(g) is hereby amended by adding after the word "revoke", the following words: "suspend, condition, limit, qualify, or restrict the license of,".

VI. Proposed amendment to Rule ME 11(g)(1).

Rule ME 11(g)(1) is hereby amended by striking and deleting the whole thereof and by substituting the following in lieu and in place thereof:

"(1) Conviction of the crime of criminal abortion or of a crime involving moral turpitude."

VII. Proposed amendment to Rule ME 62.

Rule ME 62 is hereby amended by adding after the word "suspended", the following words: "qualified, restricted,".

VIII. Proposed amendment to Rule ME 70(a).

Rule ME 70(a) is hereby amended by adding thereto after the word "limited", the words "qualified, restricted,".

Physical Conditioning Course for Children with Asthma

THE CHILD WITH asthma presents an unusual therapeutic situation. Both specific and non-specific factors must be considered in the complete management of such a child.

Allergy to a particular substance is considered a specific factor. Non-specific factors include infection, physical condition, posture, breathing methods, irritating substances and emotions.

The non-specific factors may irritate, aggravate, and complicate the course of asthma. Their management is often just as important as that of the specific allergen.

Realizing that the child with asthma is a concern not only to himself and his family, but to everyone who associates with him, the Respiratory Disease Association of Hennepin County began investigating the problem in the fall of 1965.

The Medical Advisory Committee of the Respiratory Disease Association of Hennepin County agreed, however, that more could be done for the child with asthma, particularly in relation to non-specific factors, i.e., by strengthening him physically and emotionally. This was borne out through an investigation of previous studies of children with asthma.

Feeling that a "Physical Conditioning Program for Children With Asthma" would serve the community and be a logical step for a voluntary agency to take, the Medical Advisory Committee considered a plan and its implementation. Of major significance, the prototype plan stipulated that the program was not to be considered as treatment, but as an adjunct to treatment, and that admission to the program would be only upon private physician referral. To date 162 out of 172 children who have registered have completed the course.

A $15.00 registration fee is charged to help defray the cost of the program and to obligate participants to attend regularly. In cases where the participant is unable to pay, the Respiratory Disease Association absorbs the cost.

The program has three main goals. The first goal is the improvement of the physical fitness of the participants. The youngsters are taught to breathe correctly and to improve their coordination and posture.

The second goal is of a psychological nature. The program is structured to allow the child with asthma to help himself, thus decreasing his dependency on others. As he increases his ability to do breathing exercises, he is learning how to diminish the shortness of breath associated with his asthma, thus reducing his fears and anxieties.

All too often, the child with asthma is looked upon as being "different" by himself, friends, family, and the community. As a result, his participation in society is less than optimal. Therefore, the third objective of the program is the education of the child, parent, and community to give a better understanding of the disease and its care.

Classes are held throughout the school year in the late afternoon or evening. Sessions last two hours, once a week, for eight weeks. Classes have been held at Fairview Hospitals, North Memorial Hospital, Glenwood Hills Hospital, Methodist Hospital, Ascension Club, and Penn Junior High School in Bloomington. Each class is geared to a specific age group: four to five years, six to eight years, nine to 12 years, and teenage.

Last fall, for the first time, behavior profiles were begun on the children prior to the first class, at the completion of the course, and at three, six, and 12-month intervals following the class.

The program consists of planned activities for both the children and the parents. The exercise program for the youngsters includes four phases, depending upon the location and age group:

1) Specific breathing exercises and general body conditioning
2) Karate instruction
3) One-half hour sessions in the swimming pool
4) Group discussions about asthma

For the specific breathing exercises, a two-pound sandbag is placed on the child's abdomen to demonstrate which muscles should be used in correct abdominal breathing. The child is told to inhale, lifting the sandbag up for a count of two, and then exhale, making a loud hissing sound through the teeth, for a count of six.

Most of the general conditioning exercises and calisthenics are the same as those used in school physical education programs. An exercise record book is given to each child and is used to record the number and type of exercises done each week. The record book is checked at the time of the weekly class session.

The second phase of the program is karate instruction, conducted by a qualified karate instructor and designed to improve self-confidence, coordination, and just for fun.

The third phase of the program is swimming. If a child does not know how to swim and wishes to learn, a qualified instructor works with him. Several have learned to swim during the class sessions, but the degree of success varies considerably. The purpose of including swimming in the program is to have the children feel relaxed and comfortable in the water. The general impression is that they enjoy the swimming phase of the program more than the exercises. It actually serves as a reward for exercising.

There are some definite conclusions and several impressions that can be drawn from the program to date. Almost all the children improved in some way, and very few have experienced unfavorable symptoms during the course. The majority demonstrated an increase in tolerance for exercise and activity participation. Several swam for the first time and several started to play Little League baseball. Others commented that they were able to participate in gym regularly for the first time. A significant number of the children need less medication than in previous years. Also, there has been improved school attendance, compared to a similar period during the previous year.

Children who graduate from the program are eligible to attend Camp SDIKREPUS ("superkids" spelled backwards). Camp SDIKREPUS is a two-week, away-from-home summer camp that is aimed at providing a well-rounded camping experience for the child with asthma—who very seldom is allowed to go to camp. At this point, we have three years of camping experience under our belts and are looking forward to next year.

In summary, the "Physical Conditioning Program for Children with Asthma" has been successful. The future of the program? That depends on the Medical Advisors who meet monthly to evaluate and refine the total program. Everyone involved in planning and implementing the course agrees that the program has fulfilled a real community need and that the program is a logical step for a voluntary agency to take.

Gerald W. Orr*
Minneapolis, Minnesota

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*Executive Director, Respiratory Disease Association of Hennepin County.

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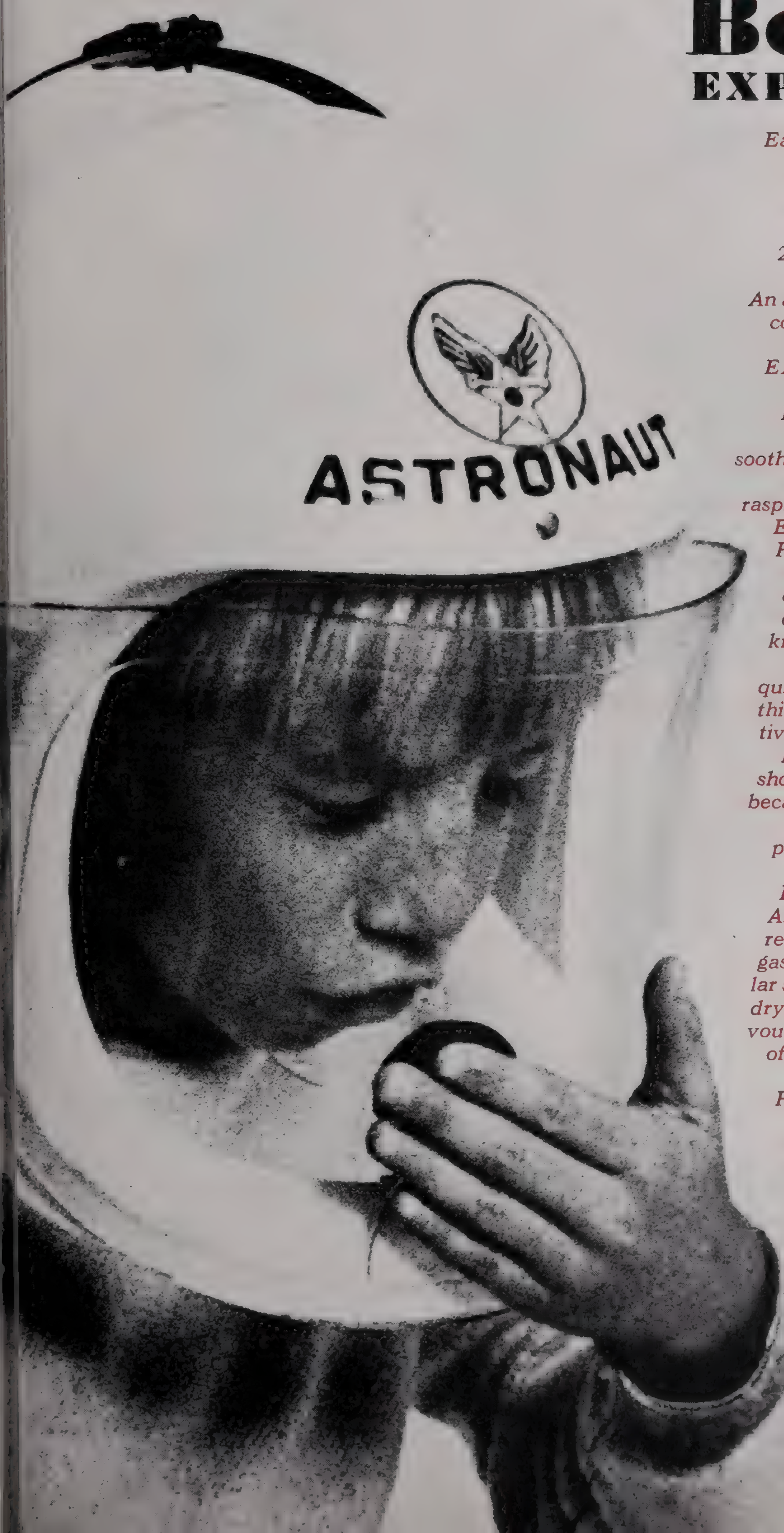

symptoms of mixed anxiety-depression are rarely clear-cut.

but they are often a clear indication for

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Before prescribing or administering, see Sandoz literature for full product information, including adverse reactions reported with phenothiazines. The following is a brief precautionary statement.

Contraindications: Severe central nervous system depression, comatose states from any cause, hypertensive or hypotensive heart disease of extreme degree.

Warnings: Administer cautiously to patients who have previously exhibited a hypersensitivity reaction (e.g., blood dyscrasias, jaundice) to phenothiazines. Phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides. During pregnancy, administer only when necessary.

Precautions: There have been infrequent reports of leukopenia and/or agranulocytosis and convulsive seizures. In epileptic patients, anticonvulsant medication should also be maintained. Pigmentary retinopathy may be avoided by remaining within the recommended limits of dosage. Administer cautiously to patients participating in activities requiring complete mental alertness (e.g., driving). Orthostatic hypotension is more common in females than in males. Do not use epinephrine in treating drug-induced hypotension. Daily doses in excess of 300 mg. should be used only in severe neuropsychiatric conditions.

Adverse Reactions: *Central Nervous System*—Drowsiness, especially with large doses, early in treatment; infrequently, pseudoparkinsonism and other extrapyramidal symptoms; nocturnal confusion, hyperactivity, lethargy, psychotic reactions, restlessness, and headache. *Autonomic Nervous System*—Dryness of mouth, blurred vision, constipation, nausea, vomiting, diarrhea, nasal stuffiness, and pallor. *Endocrine System*—Galactorrhea, breast engorgement, amenorrhea, inhibition of ejaculation, and peripheral edema. *Skin*—Dermatitis and skin eruptions of the urticarial type, photosensitivity. *Cardiovascular System*—Changes in the terminal portion of the electrocardiogram have been observed in some patients receiving the phenothiazine tranquilizers, including Mellaril (thioridazine). While there is no evidence at present that these changes are in any way precursors of any significant disturbance of cardiac rhythm, several sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients previously showing electrocardiographic changes. The use of periodic electrocardiograms has been proposed but would appear to be of questionable value as a predictive device. *Other*—A single case described as parotid swelling.

SANDOZ PHARMACEUTICALS, HANOVER, N.J. SANDOZ 69-384

Office Diagnosis of Immunologic Deficiency*

RICHARD HONG, M.D.†
Minneapolis, Minnesota

THE TRADITIONAL teaching that infection is the most important thing in alerting one to the diagnosis of immunologic deficiency is not a fruitful approach. If a child has a history of recurrent pulmonary infections, it is much more likely that he has a basic allergic diathesis rather than an immunologic problem. Other clues to an accurate diagnosis as itemized in the Table may not occur as often but, when encountered, are of much greater significance. For example, chronic moniliasis of the oroficial areas suggests the serious lymphopenic form of agammaglobulinemia in which the cellular immunity is deficient; this fatal form is also suspected if a child has progressive vaccinia. Chronic diarrhea or ulcerative colitis, especially if it occurs in the first year of life, may herald agammaglobulinemia. There are now four cases reported in which severe lymphopenic agammaglobulinemia is associated with short-limbed dwarfism.

Laboratory Studies

Hematological disorders have not been stressed as a clue to the diagnosis of immunologic deficiency; yet in recent years we have picked up countless cases of immunologic deficiency by having an immunologic study done on children who presented originally with a hematologic disorder.

Thrombocytopenia and Lymphopenia

Thrombocytopenia demands an immunologic investigation; immunologic deficiency is virtually the only cause of lymphopenia in a child other than some leukemias or Hodgkin's disease. In the newborn, lymphopenia essentially means the Swiss form of agammaglobulinemia which was, until recently, a uniformly fatal disease. There are a few pitfalls involved in the assessment of lymphopenia because the lymphopenia that we worry about is that involving the small lymphocytes. Many of the affected children have medium-sized lymphocytes and may have a total lymph count within normal (1500 total or more). Monocytosis and eosinophilia of about 10 or 15 percent should also alert suspicion. I know of no condition in the newborn period or first few months of life where you find the combination of monocytosis and eosinophilia. When you see this, even if the lymphocyte count is normal, you should look at the smear yourself; you will probably note that the lymphocytes are all of the large variety and not the little "ink dot" type.

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*Read at the Regional Continuation Course on Chronic Respiratory Diseases in Children and Adolescents at the University of Minnesota, Minneapolis, September 17, 1968.

†Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota.

Chest x-rays which show persistent pneumonia, chronic pneumonia or absence of the thymic shadow indicate immunologic deficiency.

Physical Examination

The physical examination reveals lymphoid hypoplasia. A child who has true agammaglobulinemia will not have enlarged lymph nodes and the pharyngeal tonsils will not be enlarged. General growth and development are normal. It is very interesting that children who have really severe frequent infections do not have growth retardation. Our hypogamma patients are often big strapping individuals.

Telangiectasia, especially of the eyes and ears, will be found in patients with ataxia-telangiectasia, and the syndrome here would include chronic sinusitis, bronchiectasis and usually some ataxia. Sixty percent of these show an immunoglobulin A deficiency and usually go on to have a fatal outcome after a long progressive downhill course.

Laboratory Diagnosis

Traditionally paper electrophoresis has been used to diagnose agammaglobulinemia, and it is unfortunate that many children are started on gammaglobulin therapy, using paper studies as criteria for diagnosis. Tragic complications can result: some of these children develop emotional problems and the parents acquire financial problems as the result of a mistaken diagnosis of hypogammaglobulinemia. Paper electrophoresis is worthless for the diagnosis of immunologic deficiency; it is used simply because it is readily available. Unfortunately, too many physicians shy away from an immunologic technique because they think that one has to have a $50,000.00 laboratory and a $35,000.00 technician. In fact, all one needs is $13.00 for a commercially prepared agar plate. Then all that is necessary is to draw blood or take capillary blood from the fingertip, spin it down in a hematocrit tube and break off the red cells, and then use them to fill small wells, which are already cut in the agar. The test can be done by any practitioner anywhere and is perfectly reliable. Standards from one commercial source to another may show a great deal of discrepancy; however, one is usually not as interested in hypergammaglobulinemia as in hypogammaglobulinemia. The critical level for immunoglobulin G is around 200 mg %. For immunoglobulin A and immunoglobulin M there is no need to make a decision about "borderline" values; children who have significant disease have nearly zero values (~10mg%).

Uncertainty concerning the significance of immunoglobulin values can be resolved by functional assays: measurement of specific antibody levels or titers. The development of an antibody against a known antigen proves the competence of all facets of the immune system, viz., the uptake, recognition and processing of the antigenic material followed by appropriate protein production in response to this stimulus. We commonly employ the following assays for convenience. A Schick test is easily performed and nearly all children in this country have received the appropriate immunizing series. The reagents are available from any pharmacy. In addition, isoagglutinins can be measured; the normal levels are usually ~1:20 . Further corroboration of antibody results can be obtained by immunizing with typhoid-paratyphoid antigens in the usual dosage schedule (0.5 ml sub-Q at one-week intervals for three doses). Following the immunization, most state or hospital laboratories can

TABLE

Clues to Immunologic Deficiency—History
- Recurrent Infections
- Hematological Disorders
- Skin problems—atopic dermatitis, progressive vaccinia
- Chronic diarrhea
- Ulcerative colitis
- Persistent oral moniliasis

assay for Salmonella antibodies which will be present in high titer (greater than 1:160). The value of these types of corroborative assays is illustrated by the findings in a hypogammaglobulinemic state unassociated with immunologic deficit, such as nephrosis. The gamma globulin levels in lipoid nephrosis are frequently below 200 mg%; yet with stimulation the antibody response is as high as in those patients whose gamma levels are normal. In other words, the total immunoglobulin level is less important than the specific antibody response as an indicator of immunological competence.

In a similar way, we can assess cellular immunity; we usually rely upon the standard skin tests such as the Mantoux reaction for this. The antigens employed are Old Tuberculin or Purified Protein Derivative, Candida, streptokinase-streptodernase (Varidase®) and are read at 48 hours; ten mm of induration and erythema should be present for a positive test. Unfortunately, in many instances the patient has not had a previous infection and the tests are normally negative. In this case, an actual count of the number of *small* lymphocytes is helpful. Normally, children will have over 1500 small lymphocytes/mm^3. Other assessment of the cellular system requires specialized laboratory facilities and is not within the province of the usual clinical laboratory.

Conclusions

Office diagnosis of true immunologic deficiency is feasible, and the practitioner can provide a real service and save many children from needless gamma globulin injections.

19th Century Failures

Beethoven

One celebrated patient whom medicine could not help was Ludwig von Beethoven. Plagued by intestinal disorders and approaching deafness, he made a fruitless round of physicians and surgeons, took baths, pills, and poured medications into his ears. His final illness twenty-three years later began with pneumonia after a carriage ride on a bitterly cold day but soon changed to symptoms of liver disease, which he had probably suffered from youth. His physician administered large doses of orchid tubers and repeatedly performed paracentesis. Beethoven bore his sufferings with heroic calm, but death came three months after the onset of illness. Autopsy confirmed the diagnosis of hepatic cirrhosis but showed no trace of the syphilis he had suspected to be the cause of his deafness.*

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*The Patients' Progress, Edited by Felix Marti-Ibanez, 1962.

Editor's Note: I don't suppose that the orchid tubers did much good but no doubt the paracentesis relieved him of the distress associated with his liver cirrhosis, which could have resulted from his longtime imbibing of the spirits at his numerous social activities.

O.W.H. to the Young Practitioner

You cannot and need not expect to disturb the public in the possession of its medical superstitions. A man's ignorance is as much his private property, and as precious in his own eyes, as his family Bible. You have only to open your own Bible at the ninth chapter of St. John's Gospel, and you will find that the logic of a restored patient was very simple then, as it is now, and very hard to deal with . . . Lord Bacon, Robert Boyle, Bishop Berkeley, all put their faith in panaceas which we should laugh to scorn. They had seen people get well after using them. Are we any wiser than those great men?*

---

*Oliver Wendell Holmes

Epitaph: a belated advertisement for a line of goods that has been permanently discontinued.—Irvin Cobb

King James I

Walking Pathological Museum

James was afflicted with the normal gigantic appetite of kings in those days. He ate anything and everything so long as it could be eaten; not even Charles V could have excelled his prowess. He drank, indiscriminately, beer, spirits, Spanish wines, cider, sweet French wines, and muscatel, probably mixing them all right royally. His interior organs were always too full, and he got rid of the vast surplus in whatever disgusting way, up or down, happened to be convenient.

He was subject to catarrh, and was much affected by cold and damp; he was constantly spitting, hawking, and blowing his nose. As handkerchiefs were not then in general use, I have heard that he used his sleeve or his finger and thumb, which would not add to his "clubability." He had some difficulty in swallowing, owing to some narrowing of his fauces, inherited from his mother, Mary Queen of Scots, and from his grandfather, James V of Scotland. Putting two and two together, the constant blowing of his nose and the "narrowing" of his throat, one imagines that probably the poor man suffered from adenoids and enlarged tonsils. He occasionally suffered from gravel, often accompanied by blood. He constantly suffered from another ignoble trouble, which in the course of years bled copiously. If he was specially worried in mind or body—and a king is always worried—he would become jaundiced. Whenever anything more than usually alarming occurred, the unhappy man would get diarrhoea, just like an anxious student awaiting his interview with the examiners. He used faithfully to insist on his being bled every day, until his least dignified ailment saved the doctors the trouble.

He had a truly psychasthenic dread of pain, yet hated all doctors, possibly because he had suffered too much at our hands. His teeth were all decayed, so that he could chew nothing, but had perforce to bolt his food. A man with the decayed teeth that so distinguished the "most learned fool in Christendom" would naturally in time suffer from arthritis; and in middle age this complaint so crippled him that he could hardly mount his horse. He detested purgatives, and considered that any medicine, to do good, must act upon the bowels without griping the patient; till late in life he would not even allow an enema, probably because it hurt him.

With death came, as usual, a little of that dignity that was so sadly lacking in his life. S. R. Gardiner says that he died of a fever, but it is impossible even to guess at its nature.

They held a post-mortem examination upon him, because there were the usual accusations of poisoning, apparently founded largely upon the swelling of his tongue. They found that his heart was enormously enlarged, and that in his left kidney, which was greatly shrunken, there reposed two stones, from which doubtless had come that gravel which had so afflicted him during his life. Possibly his enlarged heart and swollen tongue, together with his vast overeating and drinking, may have meant that King James I had chronic Bright's disease.*

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*C. MacLaurin: Post Mortems of Mere Mortals, 1925.

Editor's Note: With a history like that, to the diagnosis I would have added: massive obesity, hypertension, cirrhosis of the liver, esophageal varices and cardiospasm. Whatever his ignoble, least dignified trouble was could offer numerous interesting speculations.

Allergic Pulmonary Disease*

Criteria for the Diagnosis

STUART L. AREY, M.D.[†]
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BRONCHIAL ASTHMA is a form of pulmonary functional derangement resulting from reversible obstructive hyper-inflation of both lungs and characterized by paroxysmal episodes of cough and dyspnea and a prolonged expiratory phase with wheezing. Early attacks are typically relieved by sympathomimetic[‡] drugs. There may also be spontaneous remissions. The syndrome may be acute or chronic, seasonal or perennial, of single, multiple, or unknown etiology. The American College dictionary defines a wheeze as "to breathe with difficulty and with a whistling sound."

Stages of Asthma

Asthma usually presents with subjective symptoms of coughing and tightness in the chest, followed by progressive dyspnea, whistling, and expiratory wheezing until the height of the attack is reached. There are four types: I. In the simplest form there is only coughing which may be present as intermittent episodes and may persist for years. There may or may not be multiple musical expiratory rales present. II. The patient has classic symptoms with complete freedom in the intervening periods. III. The patient is always symptomatic, but there are acute exacerbations lasting two to five days. IV. There is constant severe asthma with minor changes in intensity of symptoms.

Stage I is a precursor of typical asthma. It merits good care and is not to be dismissed in the prescription for a favorite cough medicine. Some may prefer a diagnosis of allergic tracheobronchitis to avoid the stigma of a diagnosis for a time.

Etiology

Pollen

Pollen patients are worse outside, better inside, worse on bright sunny days, and have itchy eyes. In Minnesota the primary pollen is ragweed which blooms from the middle of August to frost. Grass is important in June. Tree pollens begin with elm about March 31 and end late in May. The secondary pollens, i.e., those which add to the total allergic load but do not cause symptoms by themselves, are Kochia, chenopods, Russian thistle, plantain and sorrel which bloom during the summer.

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*Read at the Regional Continuation Course on Chronic Respiratory Diseases in Children and Adolescents at the University of Minnesota, Minneapolis, September 17, 1968.

[†] Department of Pediatrics, University of Minnesota.

[‡] See Test Your Word Score page 1401.

House Dust

Housedust antigen is either the breakdown product of cotton or a parasite. It is most important when the house is closed, i.e., from September to April with the peak in January and February. These patients are worse inside, better outside. Their eyes don't itch. They tend to be worse within an hour of the time they go to bed. The mattress is a prime generator of housedust antigen.

Molds

Mold patients are worse in damp weather, worse in the low places in the road, worse in the "cool of the evening," and have symptoms after the ragweed season. They also tend to be worse when playing in the grass. There are seasonal peaks during the summer and fall. The molds disappear only when the ground is covered with snow. The primary molds in Minnesota are Alternaria and Hormodendrum. The complete list is almost endless.

Animal Emanations

Of the animal emanations, cats and dogs are most important; but cats are worse offenders than dogs because children invariably hold a kitten or cat under their nose and do a provocative test.

Foods

Foods are suspected if there is a monotonous regularity of symptoms, regardless of changes in weather, activity, or time of year. These patients tend to get worse in the middle of the night. They may have itching of the back of the nose or throat: a symptom which is almost never volunteered. Food sensitivity may be perennial, concomitant or thermal. Perennial patients have symptoms regardless of season. Concomitant food sensitivity refers to patients who have troubles only during the pollen season. Thermal food allergy is a sensitivity related to a specific food which reacts when the temperature falls below a certain level.

Family History

Over half of the children with asthma will have a positive family history of allergic disease. There seems to be a mental block about allergic disease. Superficial questioning such as: "Does anyone in your family have allergic disease?" will often fail to uncover a positive family history.

A history of previous atopic disease will favor a diagnosis of asthma: colic, spasmodic croup, infantile eczema, feeding difficulties, excessive perspiration, cracks behind the ears, itching of the nose or throat, allergic salute, perennial allergic rhinitis, seasonal pollenosis, or urticaria.

A history of sudden onset of wheezing without previous allergies is suggestive of a foreign body.

Physical Findings

In asthma we expect multiple expiratory rales throughout the chest. These rales are caused by forced expiration with the mouth open.

In mild cases they are best heard in the right anterior chest at the midclavicular line at about the level of the third or fourth rib. In long-standing severe asthma, the typical barrel chest is seen.

One of the most valuable differential points in uncomplicated asthma is the absence of clubbing of the fingers seen in contrast to the common presence in cystic fibrosis with severe pulmonary involvement.

Asthma in children under two differs from that seen in older children. Infants under two will lie on their back with marked asthma but do not exhibit the subjective distress of older children. The older child will invariably sit up and lean forward with his shoulders hunched forward during a severe attack.

Laboratory Tests

Other speakers have discussed pulmonary function, sweat tests, blood gases, eosinophilia and x-rays of the chest.

Skin Tests

Skin tests are very helpful in confirming a diagnosis of allergic disease. Scratch tests are approximately 1/100 as sensitive as intradermal tests. Either intradermal tests starting with a weak dilution as advocated by Rinkel,[1] or preliminary scratch tests followed by intradermal testing should be done. The tests for inhalants, when correlated with the history, are quite accurate; however, a few individuals will have a positive skin test for a pollen only during the pollen season.

Individual Food Test

Scratch tests or intradermal tests for foods are only 30% accurate either in a positive or in a negative fashion. Probably the most accurate test is Rinkel's individual food test. This is performed by omitting the food to be tested in all forms for four days and then feeding the food as the second meal on the fifth day, under test conditions, and noting its effect. Each test requires four days of preparation and two hours of observation. Rinkel's provocative food test is performed by injecting 0.1/ml. of a 1:100 food extract in two sites intradermally and observing the effect in twenty minutes. This test correlates well with individual feeding tests and enables one to test more foods in a shorter time with 80-90% accuracy.

Differential Diagnosis

The almost endless list can be divided with the other causes of wheezing: inflammatory, mechanical, metabolic, neurologic, and traumatic.

The following is an outline of non-allergic causes of wheezing in infants and children. The most important causes are starred.

Inflammatory:

1. Retropharyngeal abscess or peritonsillar abscess, 2. laryngitis-diphtheric or non-diphtheric, 3, epiglottitis, 4. laryngotracheobronchitis, 5. spasmodic croup, *6. asthmatic bronchitis, 7. bronchiestasis, 8. pneumonitis, *9. cystic fibrosis, *10. bronchiolitis.

Mechanical Obstruction:

1. Enlarged adenoids, polyps of the nose and larynx, 2. mucus vibrating in the respiratory passages, 3. extrinsic compression as lymph nodes or foreign body in the esophagus, *4. intrathoracic obstruction, such as a foreign body, *5. cardiovascular obstruction, such as a vascular ring and anomalies of the great vessels, 6. congenital anomalies of the respiratory tract: choanal atresia, tracheal stenosis, bronchostenosis, flaccid epiglottis, tracheomalacia, cysts of the thyroglossal duct, redundant folds of mucous membranes, subglottic hemangioma, congenital web larynx, lobar emphysema, bronchopulmonary sequestration, agenesis of lobe of the lung.

Metabolic:

Stridor of tetany.

Neurologic:

Paralysis of the recurrent laryngeal nerve and the stridor of cerebral palsy.

Traumatic:

Dislocation or fixation of the cricoarytenoid joint.

Summary

Bronchial asthma is a form of pulmonary derangement resulting from reversible obstructive hyper-inflation of both lungs. It must be differentiated from other forms of obstructive pulmonary disease, especially cystic fibrosis and foreign bodies. A family history of atopic disease is often uncovered. The chronology of the attacks should correspond with skin tests. Skin tests for inhalants correlate well with history. Skin tests for foods are only 30% accurate in either a positive or a negative fashion. The provocative food test has been very helpful in practice.

Reference

1. Rinkel, H. J. The Management of Clinical Allergy. Arch Otolaryng. 77:205, 1963.

We do not admire what we cannot understand.—Marianne Moore

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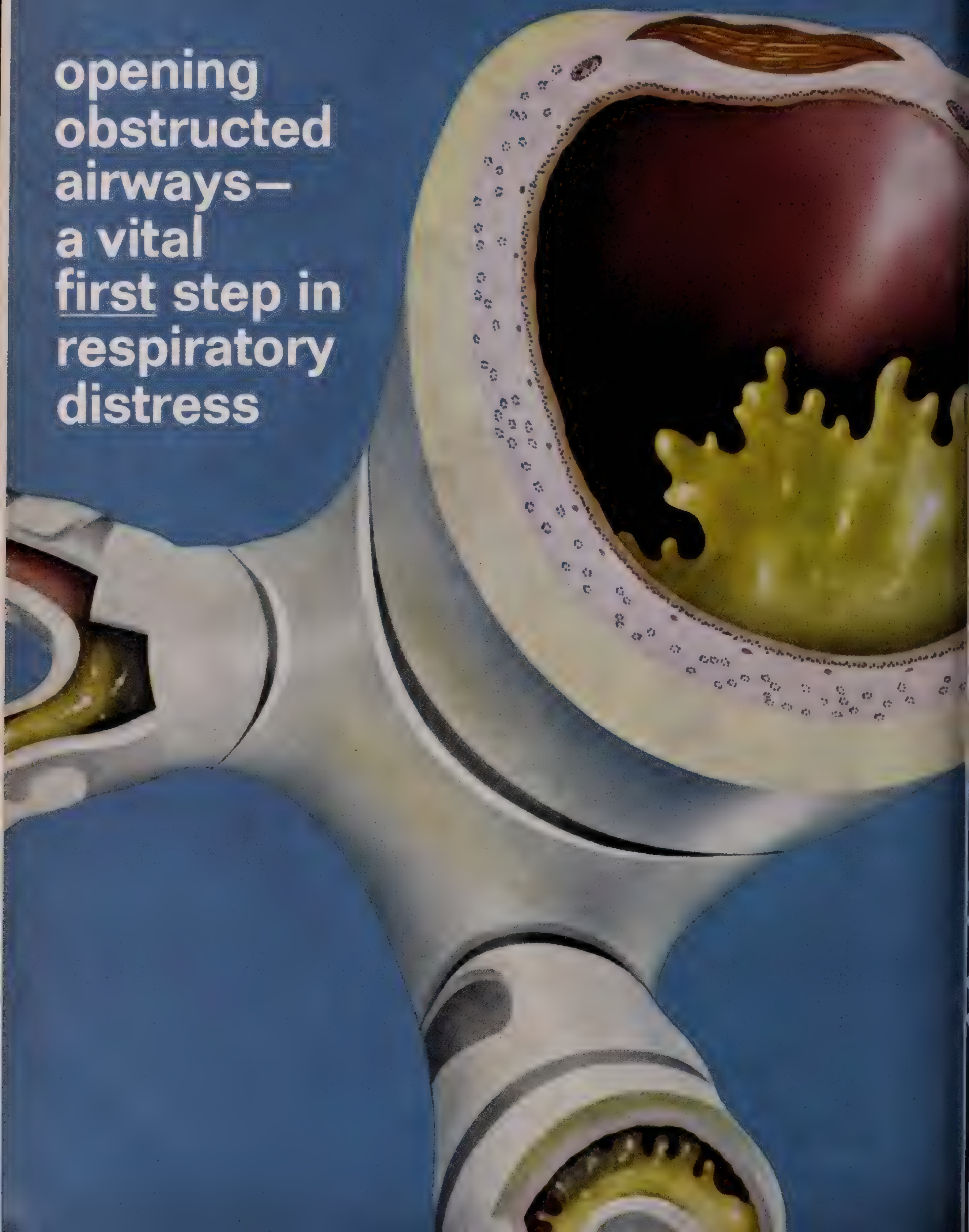

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*Simpson, D. G., comment on Fletcher, C. M., and Oldham, P. D.: CMD 33:1429-1436 (Sept.) 1966.

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Dosage: One 350 mg. capsule, 3 times daily and two at bedtime is suggested as the adult starting dose. Adjust to suit individual requirements. Daily doses above 3000 mg. are not recommended.

Contraindications: Known hypersensitivity to tybamate. Since no studies have been done with this drug in human pregnancy, it should not be used in pregnancy unless the potential benefit outweighs the risk.

Warnings: Administer cautiously to patients receiving phenothiazines or other CNS depressants or having history of convulsive seizures (See Adverse Reactions). Consider possibility of additive actions with alcohol or other psychotropic agents, particularly phenothiazines or MAO inhibitors.

Precautions: Avoid abrupt withdrawal after prolonged use, although withdrawal symptoms have not been reported to date. Exercise caution in addiction-prone individuals. If symptoms of hypersensitivity occur, discontinue at once and initiate appropriate symptomatic treatment. Avoid activities requiring optimal mental alertness if drowsiness or vertigo are present. As with any new drug, use cautiously in patients with history of drug allergies, blood dyscrasias, and hepatic or renal disease; periodic measurements of hepatic, hematopoietic and renal function should accompany prolonged and/or high doses.

Adverse Reactions: Most frequent reactions, rarely requiring discontinuation of tybamate, include drowsiness, dizziness, nausea, insomnia, and euphoria. There have been a few reports of skin rash, urticaria, and pruritus. Rare side effects include hyperactivity, fidgetiness, flushing, and tachycardia, suggesting excessive stimulation; also ataxia, unsteadiness, confusion, feeling of unreality, "panic reaction," fatigue, headache, paresthesias, vertigo, gastrointestinal disturbances, glossitis, and dry mouth. Grand mal or petit mal seizures have been reported in a few hospitalized psychotic patients receiving tybamate (up to 6000 mg. daily) together with phenothiazines and other psychotropic agents, but not with tybamate alone. Consider the possibility of rare, serious adverse reactions such as may occur with the related drug, meprobamate. If excessive amounts are ingested, gastric lavage and symptomatic therapy, including central stimulants as necessary, are recommended. Before prescribing, consult package circular.

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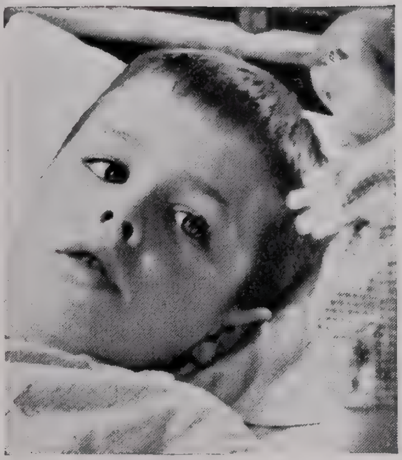

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How Cystic Fibrosis Can Be Confused with Chronic Bronchitis and Bronchial Asthma*

WARREN J. WARWICK, M.D.†
Minneapolis, Minnesota

THE CLINICIAN IS HANDICAPPED by the words he uses for these diseases. The terms "asthma" and "bronchitis" derive from Greek words, both have existed in lay and professional vocabularies from antiquity, and both carry vague connotations. Despite attempts to promote clear definitions, both terms are frequently used to describe a disease, a clinical state, a symptom, or a sign.

Asthma and Bronchitis

Asthma, when used as a designation for a disease, is equivalent to allergic asthma and bronchial asthma and encompasses a large number of more or less specific, more or less definable designations (Table). These dictionary terms are all "asthma," with a word of conjecture about the cause. These modifying words suggest scientific precision but add little to our understanding that the patient is breathing with difficulty and a wheeze except that his problem occurs in the summer, near a horse, or somewhere else. These modifying words do not suggest that the patient's asthma can be caused by mucus, edema, foreign body, infection, as well as spasm. Moreover, this list of kinds of asthma ignores the fact that asthma may be the initial or major symptom in almost every disease of the upper and lower respiratory tracts.

The clinician fares poorly when he tries to use bronchitis as a diagnosis. Bad as the term asthma is, it describes a symptom seen or heard by the clinician. Bronchitis is worse, for the supposedly inflamed bronchi are never seen, heard, or touched during a clinical examination. Use of bronchitis as a diagnostic term is, therefore, purely inferential unless a bronchoscopy is done. Perhaps "bronchitis" should be left to the pathologist who can see and touch and microscopically evaluate the bronchial tree at autopsy.

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*Read at the Regional Continuation Course on Chronic Respiratory Diseases in Children and Adolescents at the University of Minnesota, Minneapolis, September 17, 1968.

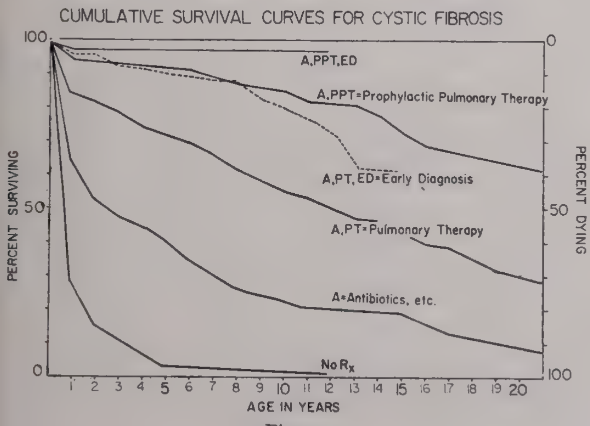
†Department of Pediatrics, University of Minnesota Medical School.

The term "chronic bronchitis" has been subjected to some restrictions by internists. These restrictions, which apply to adult medicine, give diagnostic import to bronchitis as a clinical symptom: "Chronic bronchitis refers to the condition of subjects with chronic or recurrent excessive mucous secretion in the bronchial tree." Since the pediatrician does not use this restricted definition of chronic bronchitis, he probably means only that the patient has had a chesty cough for a long time.

In an adult or child, when either clinical symptom is used for a diagnostic term, the morphologic, physiologic, etiologic, and prognostic aspects of precise diagnosis are overlooked.

Since the terms used for diagnosis provide the loci for treatment or prevention and for prognosis, the clinician who defines the topographic, morphologic, physiologic, and etiologic aspects of the patient's illness and retreats to the diagnosis, asthma or bronchitis, is in trouble. The specifics of diagnosis that are omitted by these words and the diversity of specific diseases that fall under their broad umbrellas should convince us that "asthma" and "bronchitis" do not constitute scientific diagnosis and should make us appreciate that their use as diagnostic terms has led to many disagreements concerning methods of evaluation and treatment.

The chest physician can commit no greater crime against scientific medicine than to continue to use "asthma" and "bronchitis," as Hippocrates did, to designate diseases. Many of Hippocrates' diagnoses, for example, fever and cyanosis, have been retired as diseases and are recognized to be signs or symptoms of diverse diseases. Perhaps it is time for asthma and bronchitis to surrender their claims to be diseases and to accept recognition as disease manifestations. Hence, in this article, the term "asthma" will mean labored breathing with wheezing and the term "chronic bronchitis" will mean a cough persistent for three or more months with or without production of sputum.



Figure

Cystic Fibrosis

The clinician fares better with the "classic" 30-year-old cluster of symptoms that was called cystic fibrosis of the pancreas and is now generally called just cystic fibrosis. When a child presents with failure to thrive, a ravenous appetite, a distended abdomen, wasted extremities, chronic cough with or without sputum, clubbed fingers, barrel chest, with or without signs of cirrhosis of the liver or vitamin A deficiency, few clinicians will make any other clinical diagnosis. But our modern definition also regards cystic fibrosis as the unknown metabolic defect that leads to these clinical manifestations. Therefore the clinician must now make this diagnosis in children who have only a positive sweat test with all variations of the classic symptoms from minimal to maximal. Many of these children have symptoms of asthma or of bronchitis and would without a sweat test have been given that clinical diagnosis.

The frequent dissociation of these classic clinical manifestations of cystic fibrosis from the laboratory tests that are closer to the basic genetic defect is the reason that many physicians recommend that the diagnosis of cystic fibrosis never be made in the absence of a positive sweat test and that the sweat test be done whenever a child presents with any of the classic symptoms. Cystic fibrosis has frequently been confused with asthma and chronic bronchitis because these terms are symptoms, not diseases, and because any child with cystic fibrosis can present with asthma or with bronchitis.

Since cystic fibrosis is a genetic disease identifiable by increased salinity of the sweat, the reasons why many physicians do not order a sweat test on every child with asthma or chronic bronchitis need to be studied. Most physicians consider the possibility of cystic fibrosis in these children, but reject the need for a sweat test because of one or more misassumptions concerning the disease.

False Assumptions

The following misassumptions were found in the histories of children discovered to have cystic fibrosis during the past eight years. These assumptions are misleading doctors every day; they are not strawmen.

The most common reason for an incomplete diagnostic work-up is the assumption that the child who looks well cannot have cystic fibrosis. However, all physicians caring for even moderate numbers of patients with cystic fibrosis can demonstrate patient after patient whose height and weight are average or above average and who look *too well* to have cystic fibrosis. These physicians can also demonstrate children in whom the diagnosis was made when they were *too well* to have cystic fibrosis, because a thorough physician ordered a sweat test on the basis of symptoms of asthma or chronic bronchitis.

The second false assumption is that the patient is too old to have cystic fibrosis. Our knowledge of the natural history of untreated cystic fibrosis suggests an extremely high mortality in the first few years of life (Curve Rx) so that it is therefore possible to predict that few if any patients alive today with cystic fibrosis were born prior to the development of sulfa drugs in 1939. Thus the assumption is correct that a patient over 40 years of age is too old to have cystic fibrosis.

On the other hand, all patients under forty years of age are likely to have been treated with antibiotic or chemotherapeutic agents for acute infections, and for patients with cystic fibrosis receiving such therapy the outlook is much better (Curve A). In the experience with this group of patients at the University of Minnesota, the longest interval from birth to diagnosis was 19 years in the case of a young lady who had a constant cough for 14 years and proven bronchiectasis for seven years.

Almost every Cystic Fibrosis Center has patients in the twenties, some have patients in the thirties, and some have female patients who have become pregnant and have delivered children. Therefore, if a patient has asthma or chronic bronchitis and has never had a sweat test, it would be sheer medical folly to perpetuate an incorrect diagnosis by failing to do a sweat test because the patient was in his late teens or twenties.

The third assumption is that the patient must have steatorrhea. This is based on ignorance of the fact that one of five young children with cystic fibrosis has no demonstrable pancreatic insufficiency. Furthermore, steatorrhea may not be clinically obvious, for a child with pancreatic insufficiency may restrict his fat intake and so decrease his steatorrhea. Moreover, the patient who develops pancreatic insufficiency at an older age has a relatively greater absorptive capacity of his small bowel, a decreased basal requirement for energy and a decreased requirement for growth.

The fourth assumption is that it doesn't make any difference whether or not you make the diagnosis of cystic fibrosis; the child is going to die anyway. Although the increased longevity associated with antimicrobial therapies is sufficient evidence to cast doubt on this proposition, the even greater longevity with more intensive pulmonary therapy refutes this negative view. When children with cystic fibrosis are given postural drainage, aerosol and mist-tent therapy in addition to antibiotics, a dramatic improvement in survival is observed (Curve A, PT). Furthermore, when this more intensive therapy is used continually from the time of diagnosis, the mortality is even more significantly reduced (Curve A,

TABLE

Asthma = Allergic A. = Bronchial A.

Alveolar a.
A. nocturnum
Atopic a.
Bacterial a.
Bronchial a.
Bronchitic a.
Cardiac a.
Catarrhal a.
Cheyne-Stokes a.
Elsner's a.
Essential a.
Food a.
Fuller's a.
Grinders' a.
Hay a.
Heberden's a.
Horse a.
Hyperthyroid a.
Intrinsic bronchial a.
Kopp's a.
Millar's a.
Miners' a.
Pollen a.
Potters' a.
Printers' a.
Reflex a.
Renal a.
Sexual a.
Spasmodic a.
Steam fitters' a.
Stone a.
Summer a.
Symptomatic a.
Thymic a.
Wichmann's a.

PPT). The conclusion is obvious that diagnosis of cystic fibrosis is important, for intensive treatment can effect a seven-fold increase in the number of survivors to age 20 years.

The fifth similar assumption, often used as an excuse to defer diagnosis, is that there is no need to hurry to make the diagnosis because treatment can be delayed and still be effective. This assumption is based on the frequent observation that the younger the child is at the time of symptoms leading to diagnosis, the more severe the course and complications.

Data from two large Cystic Fibrosis Centers show further improvement in survival when early diagnosis is coupled with initiation of therapy. The survival Curve A, PT, ED is to be compared with therapy delayed until the onset of symptoms (Curve A, PT), and the other Curve A, PPT, ED is to be compared with Curve A, PPT. Thus the benefits of therapy are greater when given early in the course of the disease.

The sixth assumption, that cystic fibrosis is a rare disease, has given some false comfort to the physician who doesn't do sweat tests. However, cystic fibrosis is not rare. It is the most common, fatal if untreated, genetic disease. It is transmitted by an autosomal recessive gene which is found in 5 to 6 percent of the population. It occurs in one of every 1000 to 1600 newborn infants. It is ten times more common than that in children with symptoms of asthma or bronchitis. The pediatrician who is a consultant in allergy or chest diseases and who sees five new patients a week should expect to see two patients with cystic fibrosis every year.

The seventh assumption is that sweat tests are a waste of the patient's family's money. This provides comfort only to the physician who has not analyzed the costs. Since the child with asthma or bronchitis may very likely be given an allergic workup, even started on an allergic treatment program, these costs must be considered. The cost of a sweat test is insignificant when compared to the cost of allergic treatment and to the fact that the cost of failure to provide intensive pulmonary care to the child with cystic fibrosis is progressive pulmonary destruction and early death. The money saved by not testing the 120 other children who did not have cystic fibrosis will probably be spent annually by the family of the cystic fibrosis child who had delayed treatment because the cost of treatment of a damaged lung is that much greater than the cost of prophylactic pulmonary therapy for an undamaged lung.

The eighth assumption is that every child with cystic fibrosis has a cough. Careful reading of case histories or of reports of series of cases clearly reveals that some children with cystic fibrosis have other presenting symptoms, such as steatorrhea, cirrhosis, failure to gain weight, edema, hemorrhage, heat prostration, bowel obstruction, or prolapse of the rectum.

The ninth assumption is that all sweat tests are equally good. However, authorities on cystic fibrosis agree that no screening test can be relied upon to differentiate disease from normality in a suspected patient. Clinical judgement must overrule the test if negative, since false negatives do occur and clinical judgement must seek affirmation in a quantitative sweat test if the screening test was positive, for false-positive tests also occur. Furthermore, since technologic variations can alter the range of normal values and the range of pathologic values in the sweat test, as in any laboratory test, every laboratory should establish its own ranges to aid the clinician in interpretation of sweat test results.

The tenth misleading assumption is that one sweat test is sufficient. Perhaps no false assumption is as cruel as this one, for it can lead to false-positive and false-negative diagnosis. When the clinical suspicion of cystic fibrosis exists, quantitative sweat tests should be done in *duplicate* or *triplicate*. The analytical procedures in all hospital laboratories have far greater precision than is required to make this diagnosis, for the range of typical normal values is vastly different from the range for values diagnostic of cystic fibrosis. Despite the accuracy of these instruments, on occasion a great variation may be observed in the salt content in sweat tests done simultaneously on the same individual. The error is rarely in the analytical technique, but is usually in the collection technique where a great many places for error exist. The magnitude of these errors and their random accumulation can be sufficiently great in both the positive and the negative direction to cause a single sweat test to give falsely high or falsely low values for the true salt content of the patient's sweat. The only safety for the clinician is to replicate the collection technique once or twice to reduce the chance of error to something that is clinically acceptable. When two or three sweat tests are done on a patient suspected of having cystic fibrosis and the results are comparable and in agreement as to the presence or absence of the disease, the clinician is secure in declaring the child to have or not to have cystic fibrosis.

Conclusions

The terms asthma and chronic bronchitis are inadequate for precise diagnosis of disease. Asthma should be restricted to the description of "difficult breathing with wheezing" and chronic bronchitis to a "persistent cough with or without sputum production."

Cystic fibrosis is a generalized metabolic disease in which asthma or bronchitis is the frequent first symptom.

Cystic fibrosis can be specifically differentiated from other causes of asthma and bronchitis by the sweat test. The careful clinician will have duplicate sweat tests done on every patient referred with symptoms of asthma or bronchitis.

Are Doctors Human?

The truth is that doctors *are* human; that they seem otherwise at times is purely the fault of us patients. Doctors know our deepest secrets not by some demoniac process of mental telepathy but because we insist on trotting the secrets out. We do this ostensibly to aid in treatment, actually to ease our guilty consciences or to show what rips we are or maybe just to keep the old tongue wagging.

Doctors are pampered, certainly, and yet how many of them go out of their way to attract an excess of esteem? Generally it comes to them against their will and for reasons so transparent that a two-year-old could see through them. So-and-So butters Dr. Smith to the skies at Mrs. Jones' bridge party, hoping to get a bit of free medical advice later on in the evening. Mr. Brown is also there buttering away at a great rate.

Closely connected with the pampering is the tendency to envelop doctors in an aura of infallibility. . . . Few doctors relish this role of infallibility. They know perfectly well that the real workers of miracles are the patients themselves, nine out of ten of whom meet the test of illness with astonishing heroism, persistence, patience, and self-discipline. Doctors set the stage by surgery or medicine or advice. The patient has to put the show over.

Every one of my sixteen docs has been ready and eager to admit that he is as apt to pull bloopers as any professional man or craft worker. The surgeon who yanked out my appendix frankly informed me next day that the appendix was not my trouble and that he was darned if he could find anybody who could tell him what *was* my trouble. Six months later I went through a diagnostician's clinic, garbed in a sheet like Gandhi and drinking gallons of barium. After two days of this, the head diagnostician announced his findings. "All I can discover," he said sheepishly, "is that you're allergic to turnips. To be honest with you, that doesn't mean a thing. Practically everybody I ever put through the clinic is allergic to turnips."

My present doctor has a favorite yarn about a convalescent in our hospital who hadn't seen his doctor in two years. When the doctor finally turned up, he said to the anxious convalescent, "Are you still here? Why, I meant to tell you two years back to get up and go home!"*

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*Sprague, Marshall: The Business of Getting Well, 1943.

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Inhalation Therapy*

for Chronic Obstructive Pulmonary Disease

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INHALATION THERAPY has been used empirically for many years in the treatment of chronic obstructive pulmonary disease,[1-4] but considerable disagreement still exists on the safety and efficacy of such measures as oxygen and humidity control, heated nebulizer inhalations, intermittent positive pressure breathing, mist-tent therapy and aerosol medications. Most investigators who have carried out careful studies agree on the value of these measures; but there can be little doubt that effective utilization requires an understanding of the basic physical principles involved, as well as knowledge of the pathology and pathophysiology of the disease under treatment and of the potentially harmful effects of each measure.

General Considerations and Principles

The objectives of inhalation therapy include improved and more even ventilation of the lungs, increased oxygenation of the arterial blood, more effective elimination of carbon dioxide, the wetting and thinning of bronchial mucous secretions and the deposition of locally effective medications (decongestants, bronchodilators, anti-inflammatory and mucolytic agents, and antibiotics) directly on the mucous membranes of the tracheobronchial tree.

Most of the diseases that cause obstruction of the bronchial tree do so by producing excessive or abnormally viscous secretions or a combination of these, bronchospasm, inflammation and edema of the mucous membranes, and eventually destruction and fibrosis.

Treatment

Effective treatment, in general, must be initiated before significant destruction and fibrosis have occurred and is aimed primarily at the removal of secretions, relief of bronchospasm and elimination of inflammation, edema and infection in the mucous membranes.

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*Read at the Regional Continuation Course on Chronic Respiratory Diseases in Children and Adolescents at the University of Minnesota, Minneapolis, September 17, 1968.

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Nebulization

Nebulization therapy is an extremely valuable and effective therapeutic measure which is used to wet and thin bronchial secretions and to deposit locally effective medications in the respiratory tract. It should not be confused with humidification.

Composition of Mist

The site of deposition is largely dependent on particle size of the water mist which is produced by the nebulizer, by the composition and vapor tension of the solution nebulized, and by the humidity of the air used to produce nebulization and to carry the aerosol to the respiratory tract. In general, large particles over 10 microns in diameter are deposited by inertial impaction in the upper airways,[5] and rarely penetrate beyond the nose with nasal breathing or beyond the larynx with mouth breathing. As particle mass decreases, sedimentation becomes the primary mechanism. The smaller the particles the farther they are carried in the bronchial airstream. Only particles smaller than 1-2 microns in diameter reach the bronchioles. Brownian motion, the primary mechanism for deposition of particles under 0.5 microns, is relatively unimportant in nebulization therapy.

In general, disease in the upper respiratory tract and larynx is most effectively treated with water or saline particles ranging from 5 to 10 microns in diameter. Small infants with laryngotracheal disease will often breathe through the nose and remove almost all particulate water over 6 microns in diameter before it reaches the larynx and upper trachea.[6] To treat upper airway disease a nebulizer, a high humidity room or a mist tent that produces particles with a mean particle size of 5 microns will be most effective. However, nebulizers producing particles 5 microns or more in diameter are of little value in treating disease in the periphery of the bronchial tree. To effectively treat the pulmonary lesion of cystic fibrosis, bronchitis, asthma, or bronchiolitis where involvement begins in the smaller bronchioles and extends toward the bronchi, nebulizers that produce particles in the 1-5 micron diameter range should be used, and the particle size should be stabilized by either heating and humidifying the carrier air or by reducing the vapor tension of the nebulized solution by adding propylene glycol.

Jet-Type Nebulizers

Jet-type nebulizers which produce this particle size are unsatisfactory because the aerosol produced by them contains less water (30 microliters/liter of air) than it takes to produce 100% humidity in the inspired air (44 microliters/liter) as it is warmed to 37°C in the respiratory tract.

Ultrasonic Nebulizers

Ultrasonic nebulizers are now available which produce dense aerosols (45-67 microliters/liter of air) of small and more uniform particle size. When used for mist-tent therapy these units produce a mist in the tent which contains enough water to adequately provide for humidification with a significant amount left as particulate water for deposition in the periphery of the lung. With such nebulizers distilled water can be nebulized, but inhalation of such a mist produces a cough and evidence of nasal and bronchial irritation in many patients. Normal pulmonary secretions are isotonic. When normal saline is nebulized no immediate irritation is noted, but over a period of time (weeks) it becomes apparent. This is thought to be the result of evaporation from the mist-particle which results in the deposition of salt particles is quite hypertonic. Use of ½ strength saline or 5% propylene glycol results in the deposition of a relatively isotonic solution and eliminates all evidence of irritation in most patients. A few asthmatic patients are encountered who develop bronchospasm after inhalation of any particulate material. For them nebulization therapy is contraindicated.

In utilizing nebulization therapy the density of the aerosol or mist produced, to be effective in wetting and thinning secretions, must be so dense that it is difficult to see the patient in the tent. Breathing with a rapid inspiratory flow and breathing through the nose will both increase upper airway deposition, while deep slow breathing through a wide open mouth will markedly increase deposition in the peripheral airways.

Nebulization therapy can be divided into two types: (1) Mist-tent therapy and direct inhalations from heated jet or ultrasonic nebulizers which are used over prolonged periods to add water to the pulmonary secretions, and (2)

Medication aerosol therapy which is used to administer topical medication over brief periods intermittently during the day.

Mist-Tent Therapy

Temperature and Humidity

In the hospital and most patient's homes during the respiratory disease season the temperature averages 22°C and the relative humidity less than 50% (10 microliters of water/liter of air). When air at this temperature and humidity is used to produce nebulization or to carry the mist into a tent, it quickly becomes 100% saturated with water vapor (20 microliters of water/liter of air) by evaporation of the nebulized water. Evaporation then continues to occur in the tent to replace the water vapor constantly diffusing out of the tent. A plastic tent and a cooling unit or room air-conditioner are needed regardless of the nebulizer used. The human body will increase the temperature in the tent above room temperature; also the loss of body heat by evaporation is markedly decreased in a saturated environment. Cooling the tent to 70°F or reducing the room temperature to 62-65°F will usually permit adequate heat loss by radiation and conduction.

Propylene Glycol

Because the vapor pressure of small droplets is increased by the curvature of their surface they tend to evaporate more rapidly and may be completely eliminated if plain water is nebulized. When the deposition of a larger volume of water in the peripheral bronchial tree is desired, an ultrasonic nebulizer should be used. When a smaller volume appears to be sufficient, the jet-type nebulizers may be adequate if a solution of 10% propylene glycol or 1% saline is nebulized. In any case, the nebulizer used should produce particles ranging in size from 1-5 microns in diameter.

Mist tents in general should be operated with compressed air utilizing oil-less compressors. The use of oxygen may result in oxygen concentrations in the tent which are capable of impairing the ciliary clearance mechanism of the tracheobronchial tree.[7]

Duration of Use

In treating patients with chronic obstructive pulmonary disease the mist tent can be used prophylactically as well as therapeutically. During acute flare-ups of such diseases, the patient should be kept in the tent from 10 to 18 hours/day. Continuous therapy should be avoided because it may have deleterious psychologic effects or lead to fungal infections or maceration of the skin. When such therapy is used prophylactically to prevent development or progression of chronic pulmonary disease, it is used only during sleeping hours. All of our cystic fibrosis patients and many of our patients with chronic bronchitis, bronchiectasis and asthmatic bronchitis sleep in mist tents every night at home.

Evaluation of Mist-Tent Therapy

Pulmonary Function Test Evaluation of Mist Tent Therapy and Propylene Glycol

In the initial evaluation[8] 20 patients were started on a complete therapeutic program except for omission of the mist tent. Pulmonary function studies were obtained at three-month intervals for three consecutive periods. At the end of this nine-month control period, mist-tent therapy, utilizing 2 MG II C Mist-O_2-Gen nebulizers to nebulize 10% propylene glycol in distilled water, was added to the treatment program. Repeat pulmonary function studies were performed two months later and then at four-to-five-month intervals over the next year. During the three periods before introduction of the mist tent some random variation occurred, but the changes cancelled each other and no significant changes were observed. In contrast, when the mist tent was added, significant changes in the direction of improvement were observed for all of the parameters measured except for vital capacity. The study patients had relatively mild disease with only small deficits in vital capacity; so lack of improvement in this parameter was not surprising. The changes seen in functional residual capacity, residual volume, the ratio of residual volume to total lung capacity and in maximum breathing capacity were all significant at the 0.005 level of probability. This improvement was then maintained with continued use of the mist tent and no significant changes were observed over a one-year followup period.

Tests Omitting the Mist Tent

A similar study[8] was carried out on 16 patients who were placed on the entire therapeutic program including mist-tent therapy. After their condition stabilized, as shown by pulmonary function tests over three consecutive control periods, the mist tent was eliminated from the treatment program for one month. This resulted in significant changes in the pulmonary function parameters in the direction of increased airway obstruction and over-inflation. The patients were then returned to their mist tents. Pulmonary function tests two months later and over two subsequent control intervals revealed quantitative reversal of the changes.

Evaluation of Ultrasonic Nebulization of Saline

A similar study[9] has been completed aimed at determining whether mist-tent therapy utilizing a DeVilbiss ultrasonic nebulizer using normal saline is superior to conventional mist-tent therapy utilizing jet-type nebulizers and 10% propylene glycol in sterile distilled water. For this study 41 patients were selected who had persistently abnormal pulmonary function tests despite intensive, continuous home therapy including the use of a jet-type mist tent. All of the patients were in relatively stable control as shown by pulmonary function tests obtained at three-month intervals for at least six months before the study was initiated. The only changes made were substitution of the ultrasonic nebulizer for a one-month period for the two jet-type nebulizers normally used, and a change from 10% propylene glycol in distilled water to normal saline as the nebulized solution.

The experimental design in this study was similar to that described above. All of the patients had advanced pulmonary involvement; so a tendency toward progression was seen in the mean differences for vital capacity and maximum breathing capacity during the second control interval. In contrast, after one month of therapy with the ultrasonic nebulizer, marked changes, all in the direction of improvement and all statistically significant at the 0.001 level of probability, were seen for all the parameters measured. Quantitative reversal of these changes was then observed in tests performed one month after return to the jet-type mist tent.

Saline vs Propylene Glycol

Since it was possible that the presence of salt or the absence of propylene glycol in the solutions nebulized in the ultrasonic tents contributed to the results obtained, 12 patients whose pulmonary function tests were stable on long-term ultrasonic mist-tent therapy were changed from 0.45 gm.% NaCl to 5% propylene glycol as the nebulized solution for a one-month period. This resulted if anything in slight further improvement.

Medication Aerosol Therapy

The chief purpose of intermittent aerosol therapy is the administration of potent medications in relatively small quantity. To shrink back edema of the bronchial mucosa, 1/8% phenylephrine can be nebulized. To relieve bronchospasm, a 1:200 solution of isoproterenol is effective. To decrease the growth of bacteria in the pulmonary secretions, antibiotics can be administered. To diminish the inflammatory reaction in the mucous membranes, steroids can be used. Theoretically it should also be possible to liquefy secretions by administering enzymes such as Dornovac or mucolytic agents such as N-acetylcysteine or urea; however, we have never been able to document such effects objectively.

MistO$_2$Gette or Bennett Twin Jet

We have found small nebulizers like the ETIF MistO$_2$Gette or the Bennett Twin Jet nebulizers to be safest and most effective for this form of therapy. The units can be used with either a plastic mouthpiece or a small face mask. Instruction of the patient in the techniques of breathing and the use of a mouthpiece undoubtedly lead to more effective therapy by avoiding impaction of the aerosol in the nose; but small infants and uncooperative older children can be effectively treated with a face mask. These nebulizers should be operated with the same type of compressor used for jet-type mist-tent therapy. Because of their size and requirements for a compressor and a source of electricity they cannot be carried in the child's pocket. This is a distinct advantage because it greatly decreases the probability of over-usage and dangerous toxicity.

Intermittent Positive Pressure Breathing Apparatus

In selected patients with asthma, an intermittent positive pressure breathing apparatus can be used to administer the aerosol more effectively; however, such therapy may be more harmful than beneficial in patients with cystic fibrosis who, in general, do not show a dramatic response to drugs such as isoproterenol. Because a pulmonary function test evaluation of intermittent positive pressure breathing therapy in children with cystic fibrosis revealed a progressive and eventually irreversible decrease in vital capacity and increase in air-trapping, we now use it only in the hospital for periods of less than two weeks and only on patients old enough to permit serial pulmonary function test evaluation of its effects.

Optimum Benefit from Drugs

In general, medication aerosol therapy is aimed at optimum absorption of the more potent sympathomimetic agents as well as local deposition of the decongestant, anti-inflammatory and antibiotic agents. Sympathomimetic bronchodilators are potent enough to produce a topical effect in the miniscule amounts carried by droplets less than 1 micron in diameter without producing much systemic effect. Because these droplets do not reach severely obstructed and poorly ventilated areas of the lung, the presence of some larger droplets that deposit in the larger bronchi from which the drug is absorbed to produce systemic effects is also beneficial. As the systemic effect opens the respiratory tract, more effective and even peripheral deposition of the constituents of the aerosol is achieved.

The Basic Solution

The constituents of an aerosol solution should be chosen to suit the individual patient's needs. We use a basic solution consisting of 1 part USP propylene glycol and 9 parts 1/8% phenylephrine. If significant bronchospasm exists, 0.1 to 0.5 ml. of 1:200 isoproterenol solution is added to 2 ml. of the basic solution. In patients with cystic fibrosis isoproterenol rarely produces a significant decrease in airway obstruction. When indicated, antibiotics such as methicillin (250 mg./ml.), neomycin (50 mg./ml.), polymyxin (4 mg./ml.), colistin (25 mg./ml.), carbenicillin (250 mg./ml.) and gentamycin (20 mg./ml.) are incorporated in the basic solution just before administration.

To avoid toxic effect the total dose administered over a 24-hour period should not exceed the recommended weight-calculated systemic dose. Aerosol administration of neomycin has been associated with hearing loss, especially in small infants and children under five years of age. The more potent steroids can also be administered by the aerosol route. Very small doses may produce significant pulmonary effects with minimal systemic effect; however, the systemic absorption of such drugs is readily demonstrated by the systemic effects produced by larger doses.

Aerosols of water or saline to wet and thin bronchial secretions can also be administered by direct inhalations from the nebulizer. Many older individuals who are uncomfortable or feel confined by mist-tent therapy will accept direct inhalations from either a heated, jet-type nebulizer or an ultrasonic unit. To be effective such inhalations must be continued over prolonged periods (approximately one hour) four times per day.

Precautions

All of the medications recommended above for aerosol administration are potentially harmful. Therefore, all should be prescribed carefully and their effectiveness evaluated in the individual patient clinically and, where possible, with before-and-after pulmonary function testing. Very potent drugs such as isoproterenol and potentially irritating medications such as protolytic enzymes, DNAase, N-acetylcysteine and urea should be avoided if they produce no significant beneficial effects.

Oxygen Therapy

Oxygen therapy should also be included in any discussion of inhalation therapy. One of the earliest manifestations of obstructive pulmonary disease is hypoxemia. This and the eventually associated respiratory acidosis cause an increase in pulmonary vascular resistance which eventually leads to cor pulmonale. Hypoxemia is primarily a result of uneven ventilation and abnormal ventilation-perfusion relationships in contrast to the hypercarbia and respiratory acidosis which appears only when total ventilation becomes insufficient. Increasing the O_2 content of inspired air will decrease the hypoxemia and often decrease pulmonary vascular resistance; but great care must be taken to be certain it does not result in decreased total ventilation with a resulting increase in PCO_2 and respiratory acidosis which then becomes the primary cause of increased pulmonary vascular resistance. In patients with severe chronic obstructive pulmonary disease, chronic exposure to a high PCO_2 may result in the respiratory center becoming insensitive to CO_2 and responsive only to hypoxia. In such patients the administration of O_2 eliminates the hypoxic stimulus and results in either cessation of respiration or such respiratory depression that the resulting CO_2 accumulation, narcosis and respiratory acidosis defeat all the purposes for which the oxygen was given.

Dangers

Even in patients with less severe pulmonary involvement, oxygen, especially at high partial pressures (over 450 mm.Hg.), is potentially harmful.[10] These harmful effects include a predisposition to the development of atelectasis, vascular congestion of the lungs, the appearance of an alveolar proteinaceous exudate and intra-alveolar hemorrhage, and eventual development of fibrosis. A recent study by Laurenzi et al.[7] also indicates that exposure of the respiratory tract to both low and high oxygen tensions has an adverse effect on the mucociliary clearing mechanism. This effect was observed at O_2 concentrations ranging from 25% to 100%, but in particular they caution against the administration of 100% oxygen to the hypoxic patient, since in their studies the sequential exposure of the respiratory tract to 10% and then 100% oxygen resulted in a more marked reduction in mucus flow than prolonged exposure to either concentration. It is interesting that in their studies the use of epinephrine, norepinephrine and isoproterenol by aerosol prevented or reversed this effect.

Conclusions

These studies confirmed our clinical observations and provide the first objective evidence of the value of mist-tent therapy in treating obstructive airway disease. The superiority of the ultrasonic over the jet-type nebulizer, at least for the short-term treatment of patients with advanced pulmonary disease due to cystic fibrosis, is clearly demonstrated. This is probably the result of increased deposition of water in the peripheral bronchial tree; but since the exact mechanism of action of mist-tent therapy has not been clearly elucidated, this remains conjecture.

In general, it is probably safer to administer inhalation therapy with compressed air and to utilize supplemental oxygen only when it is indicated. In most cases the benefits of supplemental oxygen can be obtained if the oxygen concentration is limited to 40% or a partial pressure below 300 mm. Hg. In all patients and especially in those with chronic respiratory insufficiency it is wise to raise the O_2 content of inspired air slowly while simultaneously monitoring its effect on respiration and on arterial PO_2, PCO_2 and pH.

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Obstructive Lung Disease*

Treatment by Physical Therapy

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THE IDEAL TREATMENT of bronchial obstruction would be the physical removal of the obstruction; however, it is not always possible or practicable to extract bronchial contents directly. Procedures have been developed, therefore, which can assist in the mobilization of intrabronchial material such as bronchial mucus and other secretions.

Initial efforts utilized mainly the principle of gravity whereby the patient was placed in one or more positions to allow drainage of individual bronchial segments.[1] By studying the anatomical disposition of the bronchial tree,[3] a series of positions were developed by which any one of the bronchial segments could be drained by placing the patient in a specific position.

At the Brompton Hospital in London, England,[2] the drainage posture was supplemented by various forms of manual vibration of the chest. As a result, there has evolved a technique of drainage combining positioning of the patient in a series of 13 positions, each related to a specific pulmonary segment together with the application of vigorous clapping alternating with manual vibration-compression applied over the area which is being drained in each individual position.[4]

Experience with cystic fibrosis has shown that a consistent form of bronchial drainage in conjunction with other measures such as vitamins, antibiotics, aerosol mist and digestive enzymes decreased the severity of pulmonary involvement in children. Doershuk and coworkers[5] reviewed a five-year multifaceted program and have shown improvement in 82% of patients treated, and in the first five years of life a decline in mortality to 3% from estimates for a similar group of untreated patients as high as 15%.

Manual Vibration-Compression

Vibration compression is done by placing the

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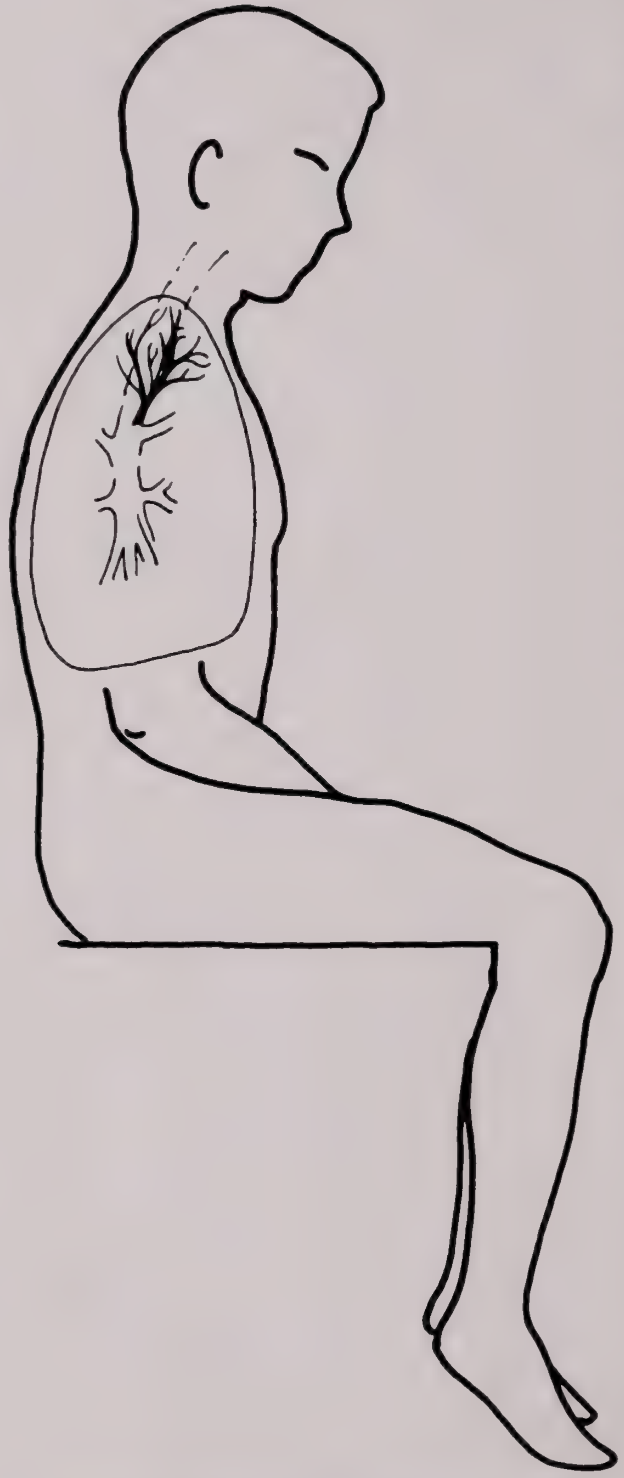

Fig. 1—Position relating to the apical bronchus, of the right upper lobe.

hands over the area of the chest to be treated, usually one hand on top of the other. For small children, using two or three fingers may be more appropriate for good localization. The hand in contact with the chest is curved to conform to the contours of the chest wall in order to obtain equal pressure throughout; isolated pressure with the finger tips or joints is usually uncomfortable and should be avoided. The vibration-compression is applied during expiration only. When the respiratory rate is rapid, the vibration should be applied every second or third breath. The hands are vibrated in a direction perpendicular to the skin surface, simultaneously with a compressive motion. The chest wall should move through an excursion of about a half inch in infants and small children to an inch or more in older children and adults. Pain or severe discomfort, over-fatigue, or interference with inspiratory efforts should be avoided. A rate of six to eight vibrations per second is generally satisfactory and appears to produce a cough effectively.

Clapping

Clapping the chest wall in the area overlying the lung segment to be treated is used alternately with vibration-compression; both hands are used and should conform to the chest contour. The chest may be protected by clothing or a towel to prevent skin irritation during the clapping, and enough force should be applied in clapping to move the chest wall. In this way, the clapping motion includes a terminal push to the chest rather than a single slap. As an alternate method, the hands may be held cupped and the cushion of air thus trapped provides protection against the pain of slapping.

The positions in which the patient is placed on the table are designed to place the segmental bronchi in as nearly vertical a position as possible. One or two pillows are used to stabilize the patient, with the table in (1) the horizontal, (2) the foot elevated 12″, (3) the foot elevated 18″ positions. At each elevation of the table the patient goes through a single rotation, stopping at the appropriate point for specific segmental treatment. Each position may be maintained three to five minutes as a rule.

Procedures With the Table Horizontal

Apical Bronchus of the Right Upper Lobe

The patient is instructed to sit upright on

All figures in this article previously published in Journal Lancet, 87:4, April 1967 by author.

the table with legs dangling (Figure 1). His back is supported by leaning against it or pressing with one hand while the other hand applies vibration compression to the infraclavicular area on the right side. He leans backward for a short period of time, then forward, then sideways to right and left during the treatment in order to drain the entire segment. Coughing is encouraged at all times, and if it begins during any part of the therapy, the procedure is interrupted and the patient's coughing assisted by supporting the lower costal and upper abdominal area with the hands.

Anterior Bronchi of the Right and Left Upper Lobes

Since the bronchi of these segments run almost directly anteroposteriorly, the patient lies on his back (Figure 2). A pillow may be placed under the knees and head for comfort. Vibration-compression and clapping may be carried out alternately over both right and left sides. Treatment is applied to the upper anterior portion of the chest at the level of the second and fourth ribs.

Posterior Bronchus of the Right Upper Lobe

From the supine position the patient turns toward the left side with the right side of the body turned forward to an angle of about 45° (Figure 3). Since the branches of this bronchus may extend in a craniad direction as well as a posterior, a slight elevation must be introduced to the chest in order to bring the inclination of the bronchus more closely to vertical. For this purpose a pillow is placed under the left axilla and left chest for support. Clapping and vibration-compression are applied to the upper posterior thorax in the general area of the lateral angle of the scapula.

Superior Bronchi of the Right and Left Lower Lobes

From the previous position a further turn of 45° brings the patient to the prone position. A pillow may be placed under the abdomen in order to flex the trunk slightly (Figure 4). Vibration-compression and clapping are applied to the back of the chest bilaterally at a level just above the lower angle of the scapula.

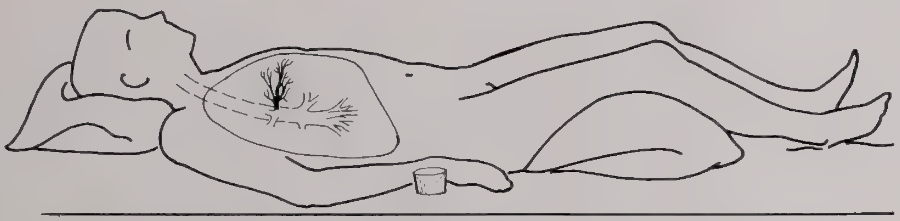

Fig. 2—Position relating to the anterior bronchi, of the right and left upper lobes with the table horizontal.

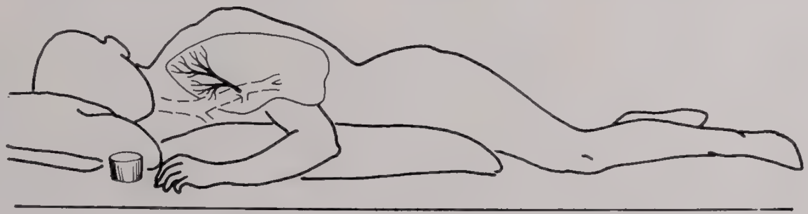

Fig. 3—Position relating to the apical posterior bronchus of the left upper lobe. The position for the posterior bronchus of the right upper lobe is a mirror image.

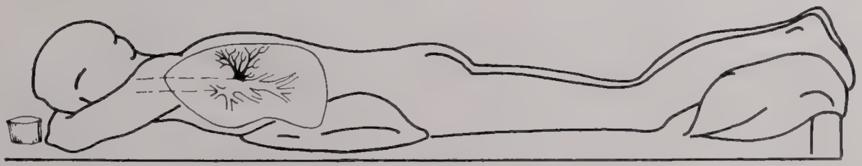

Fig. 4—Position relating to the superior bronchi of the right and left lower lobes.

Apical Posterior Bronchus of the Left Upper Lobe

Continuing the rotation by 45°, the patient now comes to lie on his right side with the left side of the body turned forward at an angle of 45°. A pillow is placed under the right axilla and right chest for support, bringing the bronchus into a vertical position. This position is a mirror image of that for the posterior bronchus of the right upper lobe (Figure 3). Treatment is applied to the corresponding area on the left side.

Procedures With Foot of Table Elevated 12 Inches

Lower Division, Left Upper Lobe (Lingular)

For the next two positions, the foot of the table is elevated 12″. The patient lies on his back, turned 45° toward the right. A pillow extending from the left shoulder to the left hip is placed along the back for support. Treatments are applied over the lateral anterior portion of the chest from the level of the third to the sixth rib.

Right Middle Lobe

Since the right middle lobe is the counterpart of the lower division of the left upper lobe, the bronchus runs in the same direction as the mirror image of the previous segment. The patient, therefore, lies on his back with his body turned toward the left side at an angle of about 45° (Figure 5). A pillow under the back extends from the right shoulder to the right hip for support. Vibration-compression and clapping are applied to the right antero-lateral portion of the chest from the third to the sixth rib.

Procedures With Foot of Table Elevated 18 Inches

The positions required to drain the segments of the lower lobes of the lungs are achieved by raising the foot of the table about 18″. Each segment is treated systematically by stopping at six different positions during a single rotation. One of the major bronchi of the lower lobes is thus placed in a vertical orientation during each of the six positions.

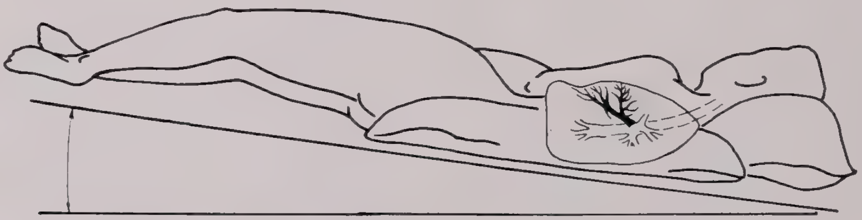

Fig. 5—Position with the foot of the table elevated 12 in., corresponding to the right middle lobe.

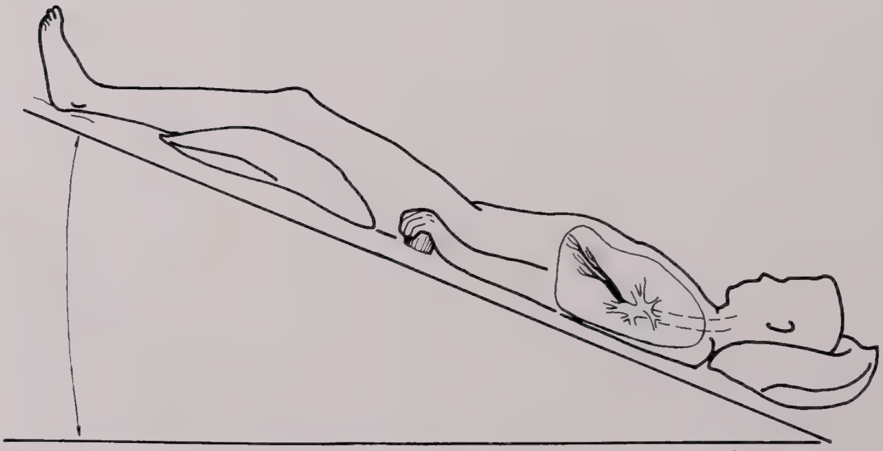

Fig. 6—With foot of the table elevated 18 in., position relates to medial basal bronchus of the right lower lobe.

Medial Basal Bronchus of the Right Lower Lobe

The patient starts in the supine position (Figure 6). Compression-vibration and clapping are applied over the lower portion of the right anterior rib cage.

Anterior Basal Bronchus of the Right Lower Lobe

The bronchus is slightly lateral to the medial bronchus. The patient turns halfway to the left, a pillow under the right side to support the back. The treatment is applied to the anterolateral aspect of the rib cage in approaching the anterior axillary line at a level between the seventh and 10th ribs.

Lateral Basal Bronchus of the Right Lower Lobe

The lateral basal segment is placed in the general area of the lateral aspect of the chest from about the sixth to the 10th rib. The patient lies directly on the left side with a pillow under the crest of the ilium to maintain the vertebral column in a straight line parallel to the table (Figure 7). The pillow should be carefully placed in order to insure proper positioning. If the pillow is placed too close to the trochanter, the lower chest will sag and the inferior portions of the basal bronchi will be inadequately oriented in the vertical direction. Treatment is applied to the right lower chest over the lateral surface.

Posterior Basal Bronchi of the Right and Left Lower Lobes

Vertical orientation of these segmental bronchi is obtained in the prone position with two pillows placed under the hips. With the elevation of the foot end of the table, the thoracic spine can be positioned at an angle of about 45° to the floor in this way. In some instances it is necessary to place a pillow and a board at the head or shoulder straps to prevent sliding

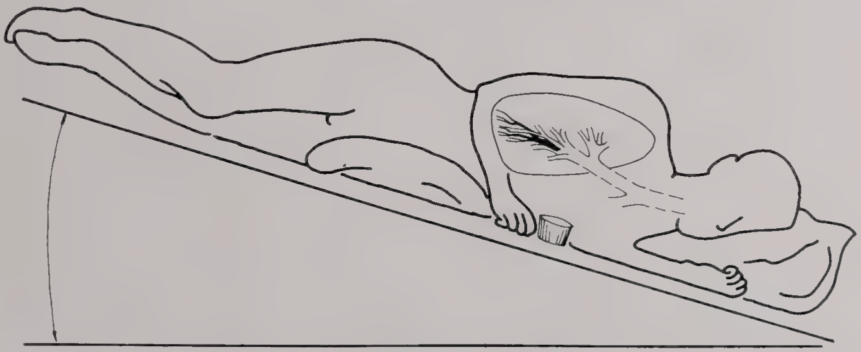

Fig. 7—With foot of table elevated 18 in., position relates to the lateral basal bronchus of the right lower lobe.

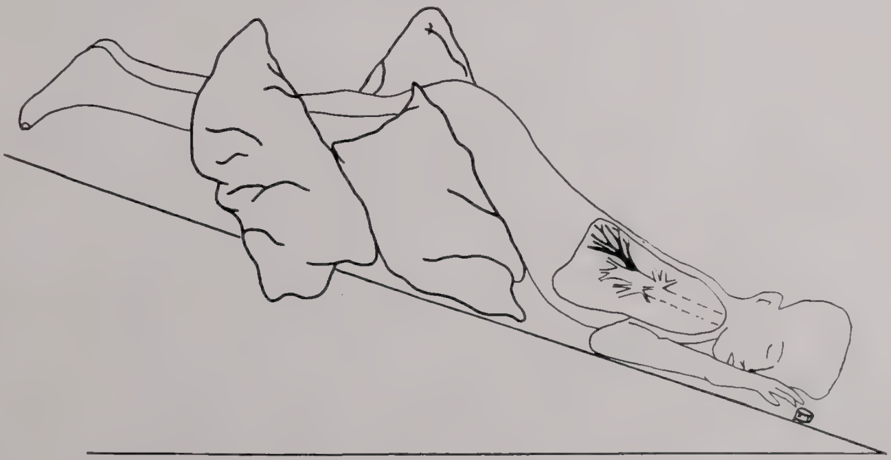

Fig. 8—With foot of the table raised 18 in., the position relates to the posterior basal bronchi of right and left lower lobes.

downward. If the legs are allowed to hang below the upper end of the table, this may also prevent sliding (Figure 8). Treatment is applied bilaterally to the lower chest posterior. This position can also be achieved in older children and adults by having the individual hang over the edge of the bed with arms on a chair or on the floor. This position will be recognized by many as that associated with the term "postural drainage" and has been in common use for treatment in adults with chronic bronchial disease such as bronchiectasis. However, since emphasis in this procedure is placed equally on the vibration-compression and clapping as well as on the positioning, the preferred term is "bronchial drainage."

Lateral Basal Bronchus of the Left Lower Lobe

This position is a mirror image of that required for the right lateral basal bronchus (Figure 7). The patient lies on the right side and a pillow is placed under the right lower ribs and ilium. Treatment is applied to the lower lateral area of the left rib cage.

Anterior Medial Basal Bronchus of the Left Lower Lobe

The patient lies on his back, with his body turned slightly to the right. A pillow along and underneath the back on the left will provide support and prevent rolling. Treatment is applied to the lower anterior portion of the left chest.

Discussion

A suitable tilting table for home use can be made of five or seven-thickness laminated plywood, hinged at one edge with a support which can be placed alternatively at two heights corresponding to the 12″ and 18″ elevation (Figure 9). Such a table may be padded and placed on the child's bed or kitchen table when in use, and can be folded conveniently out of the way during the rest of the day.

For a young infant the positions may be modified by using the lap. Tilting can be accomplished by crossing the legs and laying the

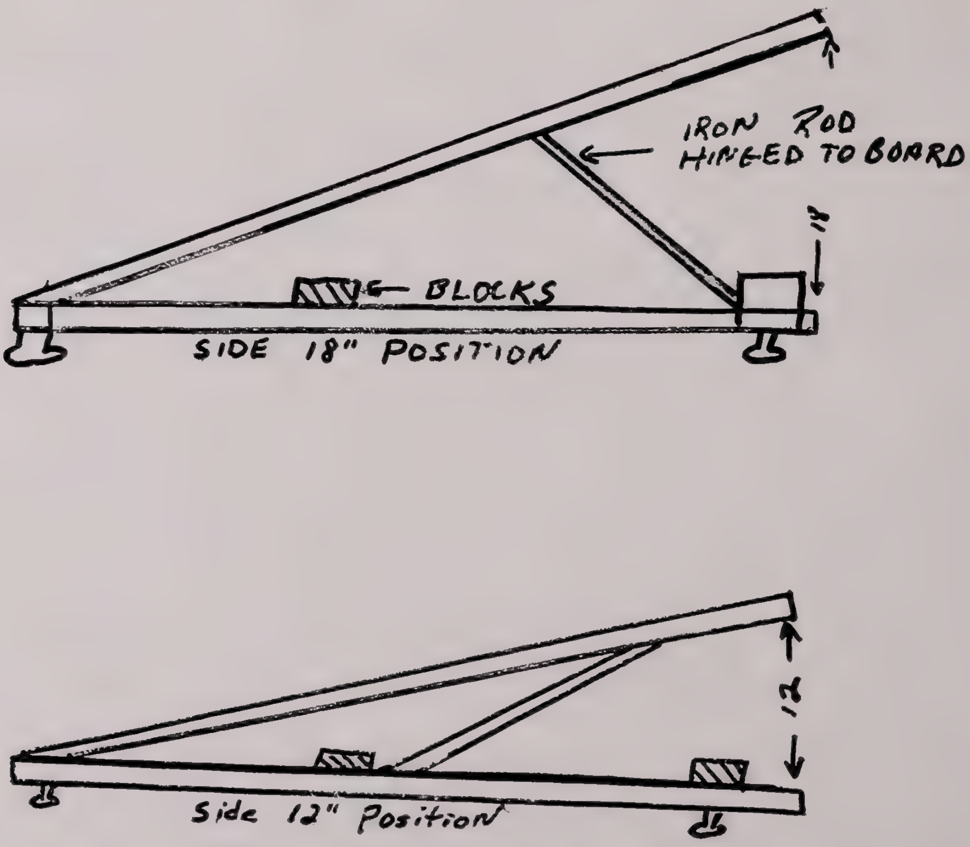

Fig. 9—Tilt board for bronchial drainage.

child across the lap in the appropriate direction or by placing one foot on a foot stool. When the baby is tilted downward, a firm grasp of the lower extremities by the elbow and forearm of the individual treating the child will prevent slipping. The feet of the child should not be against the abdomen of the adult treating, but should extend freely beyond the lap. When the respiratory rate in an infant or young child is rapid, it may be necessary to apply the compression-vibration during every second or third expiration. It is essential that no compression be applied during inspiration as this is fatiguing for the patient.

Each position should be maintained at least three to five minutes. The duration of treatment and the frequency of repetition to a particular area may be varied from two to four or more times daily depending on the degree of involvement and the rapidity of re-accumulation. When bronchial secretions are localized to a small area of one or two segments, treatment may be concentrated to these areas alone. If follow-up of a patient is close, the prescription may vary from time to time depending upon the degree and location of involvement. The complete procedure takes from 39 minutes to an hour. If this is to be carried out twice a day, there should be a distinct clinical indication, since most families will find this a serious burden if the treatment has to be carried out indefinitely. Most children with cystic fibrosis have fairly generalized involvement, and require persistent observation and treatment. When the chest is completely clear in such children, it may be useful to treat a number of selected areas on a prophylactic basis. The segments most frequently needing persistent treatment include the upper apical segments, right middle lobe, the right and left lateral basal and posterior basal segments. Treatments may be discontinued completely depending upon the rate of re-accumulation of intrabronchial mucus as observed over the period of time between examinations. Patients or their families should be instructed to resume treatment with onset of respiratory infections or spontaneous coughing.

The intensity of treatment should be limited by the clinical condition of the patient. For individuals with limited activity tolerance, dyspnea, or right heart enlargement, a full treatment program for one hour will often be exhausting, if not hazardous. The treatment should be observed and, if necessary, limited to one or two segments at a time, at intervals during the day. Treatment is best given in the morning, directly on arising, and immediately after inhalation of aerosol mist, preferably containing a mucolytic agent. In the evening, treatment is best given at least one hour after meals to avoid emesis.

The procedure of bronchial drainage has been shown to be effective in the maintenance of adequate bronchial hygiene in such chronic obstructive lung disease as bronchiectasis, chronic bronchitis, cystic fibrosis or agammaglobulinemia with bronchial disease. In addition, this procedure has been useful in acute bronchial obstructions such as postoperative atelectasis, and in bronchial obstruction associated with paralytic diseases such as Guillain-Barre disease. In the latter situation, the bronchial drainage procedure should be used together with catheter suction because of the inadequate coughing mechanism.

The procedure may be carried out by physical therapists, nurses, or their aides who have been instructed in the technique. Since many patients require a prolonged period of treatment at home it has been found useful to instruct parents, family members, or other nonprofessionals in the procedure. With careful instructions, supervision, and subsequent review of their application of the treatment, continued therapy at home has been maintained satisfactorily.

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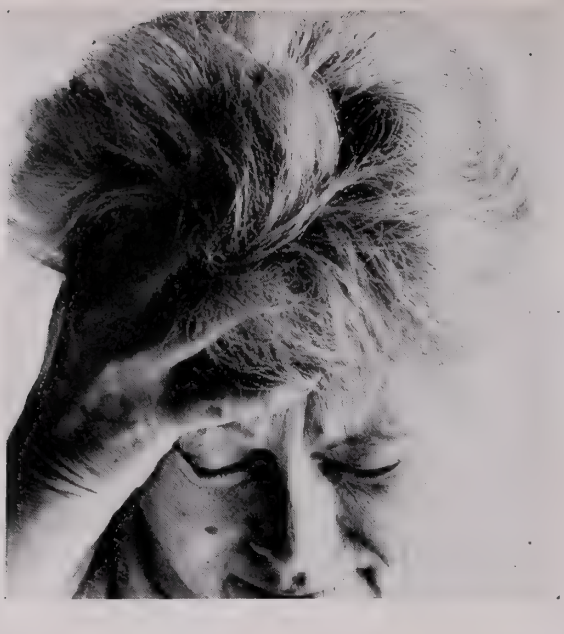

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SIDE EFFECTS: Similar to those reported with either constituent alone. **Perphenazine:** Should not be used indiscriminately. Use caution in patients with history of convulsive disorders or severe reactions to other phenothiazines. Likelihood of untoward actions greater with high doses. Closely supervise with any dosage. Side effects may be any of those reported with phenothiazine drugs: blood dyscrasias (pancytopenia, thrombocytopenic purpura, leukopenia, agranulocytosis, eosinophilia); liver damage (jaundice, biliary stasis); extrapyramidal symptoms (opisthotonos, oculogyric crisis, hyperreflexia, dystonia, akathisia, dyskinesia, parkinsonism) usually controlled by the concomitant use of effective antiparkinsonian drugs and/or by reduction in dosage, but sometimes persist after discontinuation of the phenothiazine; severe, acute hypotension (of particular concern in patients with mitral insufficiency or pheochromocytoma); skin disorders (photosensitivity, itching, erythema, urticaria, eczema, up to exfoliative dermatitis); other allergic reactions (asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions); peripheral edema; reversed epinephrine effect; endocrine disturbances (lactation, galactorrhea, disturbances of menstrual cycle); grand mal convulsions; cerebral edema; altered cerebrospinal fluid proteins; polyphagia; paradoxical excitement; photophobia; skin pigmentation; failure of ejaculation; EKG abnormalities (quinidine-like effect); reactivation of psychotic processes; catatonic-like states; autonomic reactions such as dryness of the mouth, headache, nausea, vomiting, constipation, obstipation, urinary frequency, blurred vision, nasal congestion, and a change in the pulse rate; hypnotic effects; pigmentary retinopathy; corneal and lenticular pigmentation; occasional lassitude; muscle weakness; mild insomnia; significant unexplained rise in body temperature may suggest intolerance to perphenazine, in which case discontinue. Antiemetic effect may obscure signs of toxicity due to overdosage of other drugs or make diagnosis of other disorders such as brain tumors or intestinal obstruction difficult. May potentiate central nervous system depressants (opiates, analgesics, antihistamines, barbiturates, alcohol), atropine, heat, and phosphorous insecticides. **Amitriptyline:** Careful observation of all patients recommended. Side effects include drowsiness (may occur within the first few days of therapy); dizziness; nausea; excitement; hypotension; fainting; fine tremor; jitteriness; weakness; headache; heartburn; anorexia; increased perspiration; incoordination; allergic-type reactions manifested by skin rash, swelling of face and tongue, itching; numbness and tingling of limbs, including peripheral neuropathy; activation of latent schizophrenia (however, the perphenazine content may prevent this reaction in some cases); epileptiform seizures in chronic schizophrenics; temporary confusion, disturbed concentration, or transient visual hallucinations on high doses; evidence of anticholinergic activity, such as tachycardia, dryness of mouth, blurring of vision, urinary retention, constipation, paralytic ileus; agranulocytosis; jaundice. The antidepressant activity may be evident within 3 or 4 days or may take as long as 30 days to develop adequately, and lack of response sometimes occurs. Response to medication will vary according to severity as well as type of depression present. Elderly patients and adolescents can often be managed on lower dosage levels.

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Disc Sensitivities in the Selection of Antibiotics*

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Minneapolis, Minnesota

THERE ARE RELATIVELY few cases whereof one can say with surety that a certain antibiotic will inhibit or kill all strains of a particular bacterial species, independent of the body location where the strain may be causing an infection. To ascertain the appropriate antibiotic therapy for most types of bacterial infection, one must employ some method of determining which antibiotic and how much of it will be required to effectively eradicate the organism. This can be accomplished in most cases, however, by *in-vitro* testing.

Background

Of the three methods available,‡ the plate diffusion test employing antibiotic-impregnated paper discs seems the most utilitarian for the usual hospital laboratory and also for use in the physician's office, should conditions allow for some limited bacteriologic endeavors. Indeed, most clinical microbiology laboratories in this country now employ the paper-disc method using the commercially available discs.[2] For the purposes of this paper, all further discussion will pertain only to the plate diffusion method, using the paper discs.

Since the paper-disc method was first introduced,[3] a number of different protocols and methods have been advocated.[2-5] Other than differences in inoculum size or media used, the biggest variation of method has been in the use of the single disc or multiple discs for each antibiotic tested. The single high-potency disc method provides the most reasonable approach to disc testing and seems to offer the best correlation with dilution techniques.[1,2,6,7]

Disc Sensitivity

In all sensitivity testing methods, the size of the inoculum will affect the end result to a greater or lesser degree, depending on the method. The rigidity of standardization of the inoculum determines the reproducibility of zone readings. The use of the turbidity standard and the swabbing technique, as outlined subsequently, offers the greatest facility. Though variability may be slightly greater than with some other methods,[8,9] this variability does not unduly alter the final interpretation with respect to reproducibility, nor does it change beyond acceptable limits the interpretation of any single determination.

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*Read at the Regional Continuation Course on Chronic Respiratory Diseases in Children and Adolescents at the University of Minnesota, Minneapolis, September 17, 1968.

†Assistant Professor of Laboratory Medicine and Pediatrics, and Director, Diagnostic Microbiology Laboratories, University of Minnesota Hospitals.

‡The broth dilution, the agar dilution and the plate diffusion methods.

The medium used will also affect interpretation of results, due to production variability, diffusion differences and growth patterns. The medium recommended by the World Health Organization (WHO) expert committee[9,10] and by the proponents[2] of the method subsequently described is the Mueller-Hinton medium. As stated in the World Health Organization report:[10] "Mueller-Hinton medium was selected because of its good reproducibility, because of the positive experience of some members of the working party who have used it in their routine work, and because its production is potentially less variable than media which involve enzymatic digestive processes."

Sensitivity Technique

The disc-testing method used in the University of Minnesota Diagnostic Microbiology Laboratories is a slight modification of the method described by Bauer, Kirby, Sherris and Turck[2] of the University of Washington.

Five isolated colonies of an organism are picked from the original culture plate and are inoculated into a culture tube containing 3-5 ml of a suitable nutrient broth (Mueller-Hinton, tryptose phosphate, trypicase soy broths, etc.). Incubation then progresses for a sufficient period to allow for growth to be visible in the form of cloudiness or turbidity in the medium. This usually requires three to five hours, but the process may be enhanced for certain slow-growing organisms either by using a heavy initial inoculum or by longer incubation. An overnight broth culture may also be used. The culture suspension is then diluted to a density visually equivalent to that of a McFarland #0.5 standard. This dilution can be achieved by adding normal saline or water to the culture, or by adding a portion of the culture to a tube of saline. A McFarland #0.5 standard can be prepared by adding 0.5 ml of one per cent $BaCl_2$ to 99.5 ml of one per cent H_2SO_4 (0.36N).

Once the culture has been standardized, the Mueller-Hinton plate to be used should be streaked within 15 minutes by dipping a sterile cotton swab into the standardized and well-mixed suspension. The swab is rotated against the inside of the tube to remove excess suspension and is then streaked evenly across the Mueller-Hinton plate in three planes. Then the plates are allowed to sit for about five minutes to allow the inoculum to dry. The discs are then applied about 2 cm from the outer edge of the plate and sufficiently far apart so that inhibition zones do not overlap (about nine discs in the outer circle of discs on the 15 cm petri plate). Application is accomplished by means of applicators or with flamed and cooled forceps. The discs are then pressed firmly in place and the plates incubated. In this method it is important to incubate immediately so as not to alter results by allowing drug pre-diffusion, which will alter zone sizes.

Preparation of Plates

If one is to employ the method outlined here, it should be followed exactly; otherwise one cannot use with reliability the table included for interpretation. This method has been standardized using the large 15 cm petri plates. The use of regular 9-10 cm plates will probably result in a heavier inoculum, due to placing more organisms on a smaller surface area and thus introducing possible error in interpretation. The medium should be 5-6 mm in depth, necessitating the use of 65-75 ml of agar per 15 cm plate. Before being streaked, the plates should be dried for approximately 30 minutes in an incubator by inverting each plate and partially removing the cover portion which in the inverted position will be on the bottom. Ideally plates are used the same week they are prepared.

Discs

Discs should be obtained from a reliable supply house, where proper conditions of storage exist. It may be unwise to accept discs from drug company detail men due to the unknown aspects of the storage of their discs, since heat, freezing and thawing, and moisture can all hasten deterioration. All of these conditions may exist in the trunk of the detail man's car, depending on the season of the year.

Certain discs seem less stable than others. Notable in this regard are ampicillin and methicillin. We not infrequently receive from other laboratories specimens reported to be resistant to one or the other of these antibiotics, and testing with our discs and with dilution methods demonstrates strain sensitivity. We store our discs in the frozen state until we are ready to use them. While a cartridge is being used, it is kept in a desiccator bottle in the regular refrigerator. When removed from the refrigerator the discs are kept in the desiccator bottle until they have equilibrated to room temperature. This prevents moisture of condensation from forming in the cartridge and on the discs. After use the cartridge is replaced in the jar and re-refrigerated but never refrozen.

Incubation and Interpretation

Plates are incubated at 35-37°C overnight, and the diameters of the zones of inhibition around the discs are measured, using a ruler on the under surface of the plate or with calipers near the surface of the agar. In our laboratory we use the Fisher-Lilly Antibiotic Zone Reader (Fisher Scientific, No. 7-906 V2). After measuring zone size, one refers to the table of diameters (Table) to determine if the organism is

TABLE

Zone Size Interpretative Chart[2,11,12]

Antibiotic or Chemotherapeutic Agent		Disc Potency	mm Inhibition Zone Diameter to nearest mm		
			Resistant	Intermediate	Sensitive
Ampicillin	Gram-negative and enterococci	10 µgm	11 or less	12 - 13	14 or more
	Staphylococci and highly penicillin-sensitive organisms	10 µgm	20 or less	21 - 28	29 or more
	*Hemophilus**				20 or more
Bacitracin		10 U	8 or less	9 - 12	13 or more
Cephaloridine		30 µgm	11 or less	12 - 15	16 or more
Cephalothin		30 µgm	14 or less	15 - 17	18 or more
Chloramphenicol		30 µgm	12 or less	13 - 17	18 or more
Colistin		10 µgm	8 or less	9 - 10	11 or more
Erythromycin		15 µgm	13 or less	14 - 17	18 or more
Gentamicin*		10 µgm	—	—	13 or more
Kanamycin		30 µgm	13 or less	14 - 17	18 or more
Lincomycin		2 µgm	9 or less	10 - 14	15 or more
Methicillin		5 µgm	9 or less	10 - 13	14 or more
Nafcillin and Oxacillin*		1 µgm	10 or less	11 - 12	13 or more
Nalidixic acid†		30 µgm	13 or less	14 - 18	19 or more
Neomycin		30 µgm	12 or less	13 - 16	17 or more
Novobiocin‡		30 µgm	17 or less	18 - 21	22 or more
Nitrofurantoin†		300 µgm	14 or less	15 - 16	17 or more
Oleandomycin		15 µgm	11 or less	12 - 16	17 or more
Penicillin-G	Staphylococci	10 U	20 or less	21 - 28	29 or more
	Other organisms	10 U	11 or less	12 - 21+	
Polymyxin-B		300 U	8 or less	9 - 11	12 or more
Streptomycin		10 µgm	11 or less	12 - 14	15 or more
Sulfonamides*§†		300 µgm	12 or less	13 - 16	17 or more
	Meningococcus	300 µgm	36 or less	37 - 39	40 or more
Tetracycline		30 µgm	14 or less	15 - 18	19 or more
Vancomycin		30 µgm	9 or less	10 - 11	12 or more

*Tentative standards.

†Urinary tract infections only.

‡Not applicable to blood containing media.

§Any of the commercially available 300 or 250 µgm sulfonamide discs can be used with the same standard of zone interpretation.

+This category includes some organisms such as enterococci which may cause systemic infections treatable by high doses of penicillin G.

sensitive, intermediate or resistant to the particular antibiotic being tested. The discs themselves measure 6 mm; hence no zone would be recorded as 6 mm. For measuring zones, the margins separating areas of visible growth and no growth are used for end points, except with the sulfonamides. Since organisms grow through several generations before inhibition with sulfonamides takes place, slight growth is disregarded and the margin of heavy growth (80% inhibition) is used for an end point. Bauer et al.[2] point out that this technique is satisfactory for sensitivity testing of all organisms against sulfonamides except group A beta-hemolytic streptococci. Spreading *Proteus* will form a thin veil of swarming around the discs. This swarming is disregarded, and one uses the margin of heavy growth for zone site measurement. If colonies appear within any inhibition zone, the culture should be checked for purity.

For testing *Hemophilus*, streptococci, enterococci, and certain other fastidious organisms, 5% sheep blood or human blood should be added to the Mueller-Hinton agar. The blood should be "chocalatized," or Fildes digest or Supplement B (Difco) added for *Hemophilus.*

The standards in the Table have been developed for rapidly growing pathogens. The slower-growing organisms have been less completely studied, but one can make the comment that due to slower growth, greater diffusion of antibiotics takes place. Thus, zones with these organisms tend to be larger, and this should be taken into account in interpreting results. It has been our experience that a 2 to 6 mm difference in zone size is not uncommon with organisms allowed to incubate only after pre-diffusion of the antibiotic has occurred. We therefore realize that such a deviation may also be manifest in the results obtained with slow-growing organisms.

Comments

It should also be pointed out that this method is considered invalid at present for testing *Neisseria gonorrhoeae.*[11] For sulfonamide testing of meningococci, the data of Bennett, Camp and Eickhoff[12] are used for zone size interpretation and are included in the Table.

If one uses a method based upon testing sufficient bacterial strains by comparing zone sizes with dilution studies, and if one has available the regression curves thus obtained, it is possible to relate zone size to minimal inhibitory concentration within a given range, depending on the scatter points on the regression curve for a specific antibiotic. For example, this is possible for us, using the regression tables worked out in our laboratory and in the laboratories of Dr. John C. Sherris.[11] These scatter-gram regression curves have been derived by using over 100 total strains of several different species of bacteria for each antibiotic.

The utility of this method is greatly enhanced by following the general protocol closely. The interpretive zone diameters in the Table have been closely worked out by using the agar dilution method for comparison,[2] and by relating the regression values to blood levels obtainable with the commonly used dosage schedules.

Antibiotics

The choice of antibiotics to be tested may be left entirely to the individual doctor; or they may be a matter of laboratory routine for gram-negative or gram-positive bacterial classes, or may be set by bacterial species. In our laboratory, if the physician has no preference of antibiotics to be tested, we employ routines dictated by the bacterial species to be tested.

Clinical Value

The clinical application evolves from the fact that all of us in clinical medicine deal with the use of antibiotics and are therefore in the position of using sensitivity data to guide our therapy. It would seem, then, that we would want to rely on the data we are receiving. Unfortunately, many laboratories do not use standardized methods for testing, and many do not have a solid basis on which to interpret the results of their particular method. Your familiarization with the need for a standardized method is hopefully enhanced at this point.

"The technique should be used exactly as described because, although it has considerable flexibility, changes in conditions may combine to produce inaccuracies; it should be particularly stressed that the zone sizes in the table are *only applicable to the use of Mueller-Hinton medium and to disc contents listed in the* *table.*"[2]

It would perhaps be in the best interests of the physician's clinical practice to become acquainted with the methods used in his hospital or commercial laboratory for sensitivity testing; even bolder yet, it may even be proper for him to insist on a standardized method based upon sufficient data to justify the interpretations reported.

Summary

For over-all ease, accuracy and utility the disc diffusion method of antibiotic sensitivity testing is the method of choice for most laboratories. However, to be able to report valid results, the method used must be standardized and based upon sufficient accumulated data to justify the interpretations and to insure reproducibility. The single high-potency disc method described herein meets these criteria and is currently in wide use in this country. Physicians relying on data from sensitivity testing should insist that there be justification of methods and reproducibility of results through standardization in any laboratory upon which they rely for sensitivity results.

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It's the Law

Physician Not Liable for Postoperative Infection

A patient underwent removal of a torn cartilage of the knee. A postoperative staphylococcus infection developed necessitating draining and eventual removal of the patella. This resulted in a permanently stiffened knee.

The court ruled that the physician was not liable for the infection and, hence, not for the resulting disability.

Johnson v. Myers, 165 S.E.2d 739 (Ga., Nov. 12, 1968; rehearing denied Dec. 5, 1968). The Citation 19:3, May 15, 1969.

Drink

Walking into a bar optimistically and coming out misty optically accentuates the inevitable.—Typographical Journal

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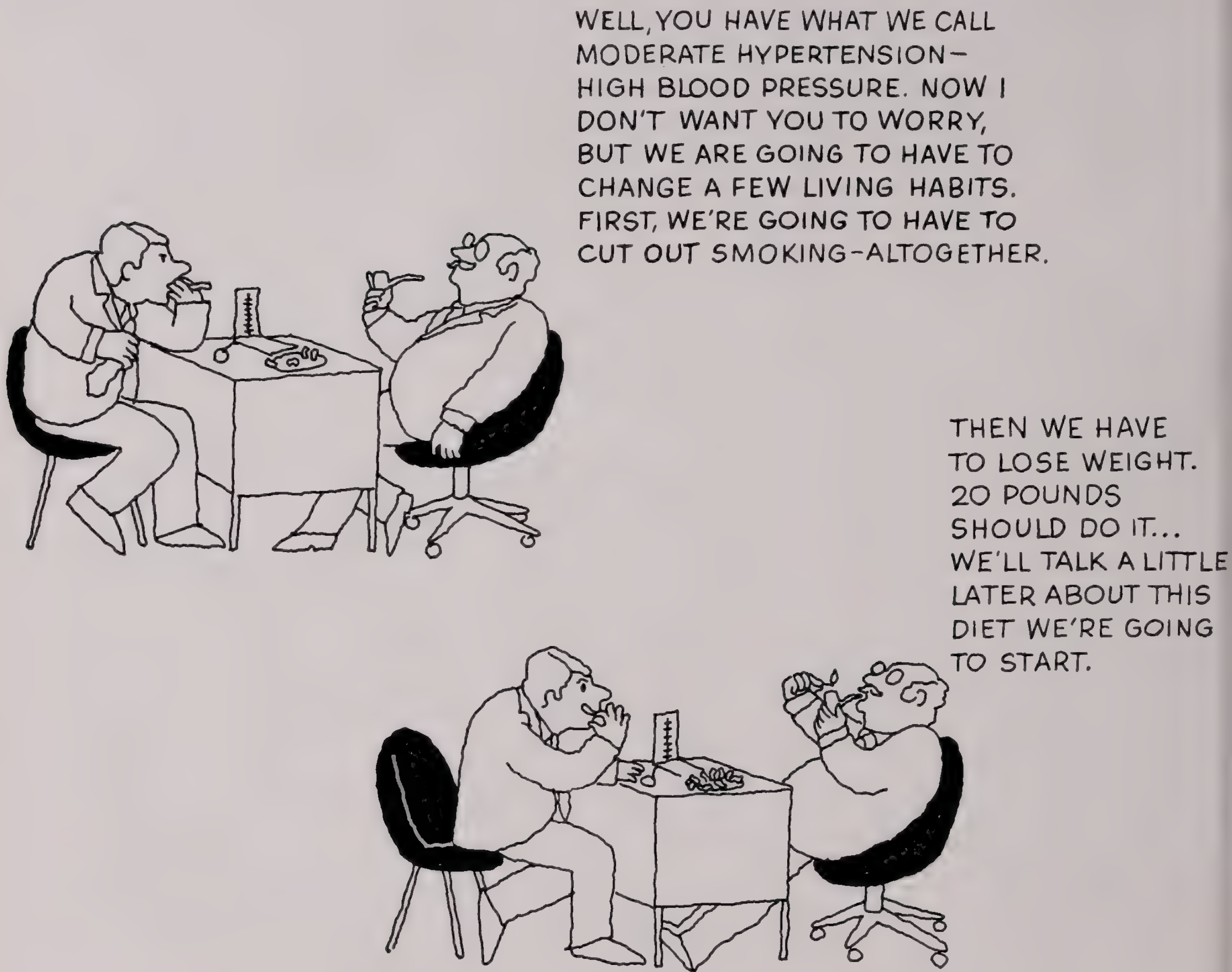
If nominated I will not accept; if elected I will not serve.—William Tecumseh Sherman, 1884

The Apprehensive Hypertensive


WELL, YOU HAVE WHAT WE CALL MODERATE HYPERTENSION— HIGH BLOOD PRESSURE. NOW I DON'T WANT YOU TO WORRY, BUT WE ARE GOING TO HAVE TO CHANGE A FEW LIVING HABITS. FIRST, WE'RE GOING TO HAVE TO CUT OUT SMOKING-ALTOGETHER.
THEN WE HAVE TO LOSE WEIGHT. 20 POUNDS SHOULD DO IT... WE'LL TALK A LITTLE LATER ABOUT THIS DIET WE'RE GOING TO START.

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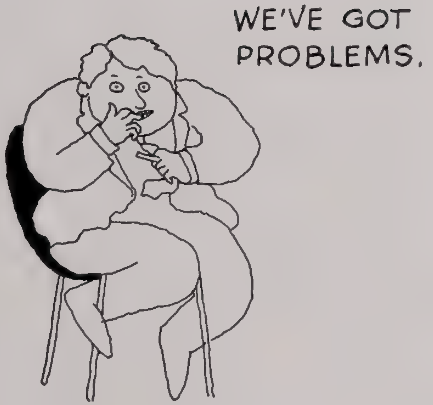
chlorthalidone 50 mg.
reserpine U.S.P. 0.25 mg.

Regroton®: chlorthalidone 50 mg., reserpine U.S.P. 0.25 mg. *Indications:* Hypertension. *Contraindications:* History of mental depression, hypersensitivity, and most cases of severe renal or hepatic diseases. *Warning:* With the administration of enteric-coated potassium supplements, which should be used only when adequate dietary supplementation is not practical, the possibility of small-bowel lesions (obstruction, hemorrhage, and perforation) should be kept in mind. Surgery for these lesions has frequently been required and deaths have occurred. Discontinue coated potassium-containing formulations immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occur. Discontinue one week before electroshock therapy, and if depression or peptic ulcer occurs. *Use in pregnancy:* Because chlorthalidone may cross the placental barrier and appear in cord blood and thiazides may appear in breast milk, this drug should be used with care in pregnant patients and nursing mothers. When used in women of childbearing age, the potential benefits of the drug should be weighed against the possible hazards to the fetus. Use of chlorthalidone may result in fetal or neonatal jaundice, thrombocytopenia, and possibly
other adverse reactions which have occurred in the adult. Increase
respiratory secretions, nasal congestion, cyanosis and anorexia ma
occur in infants born to reserpine-treated mothers. *Precautions:* Antihy
pertensive therapy with this drug should always be initiated cautious
in postsympathectomy patients and in patients receiving ganglion
blocking agents, other potent antihypertensive drugs, or curare. Reduc
dosage of concomitant antihypertensive agents by at least one-half. T
avoid hypotension during surgery, discontinue therapy with this age
two weeks prior to elective surgical procedures. In emergency surger
use, if needed, anticholinergic or adrenergic drugs or other supporti
measures as indicated. Because of the possibility of progression
renal damage, periodic kidney function tests are indicated. Discontinu
if the BUN rises or liver dysfunction is aggravated. Hepatic coma ma
be precipitated. Electrolyte imbalance, sodium and/or potassium d
pletion may occur. If potassium depletion should occur during therap
the drug should be discontinued and potassium supplements give
provided the patient does not have marked oliguria. Take particular ca
in cirrhosis or severe ischemic heart disease and in patients receivir

WE'VE GOT TO GET PLENTY OF REST AND TRY TO AVOID SITUATIONS THAT MAKE US ANXIOUS OR TENSE. AND WE'LL TAKE MEDICINE TO LOWER OUR BLOOD PRESSURE AND CALM US DOWN.


WE'VE GOT PROBLEMS.

and allay anxiety in hypertension

corticosteroids, ACTH, or digitalis. Severe salt restriction is not recom-nended. Use cautiously in patients with ulcerative colitis or gallstones (biliary colic may be precipitated). Bronchial asthma may occur in susceptible patients. *Adverse Reactions:* The drug is generally well olerated. The most frequent side effects are nausea, gastric irritation, vomiting, diarrhea, constipation, muscle cramps, headache, dizziness and acute gout. Other potential side effects include angina pectoris, anxiety, depression, bradycardia and ectopic cardiac rhythms (espe-cially when used with digitalis), drowsiness, dull sensorium, hypergly-cemia and glycosuria, hyperuricemia, lassitude, restlessness, transient nyopia, impotence or dysuria, orthostatic hypotension which may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics, leukopenia, aplastic anemia, skin rashes, thrombocyto-penia, agranulocytosis, nasal stuffiness, increased gastric secretions, nightmare, purpura, urticaria, ecchymosis, weakness, uveitis, optic itrophy and glaucoma, and pruritus. Eruptions and/or flushing of the kin, a reversible paralysis agitans-like syndrome, blurred vision, con-unctival injection, increased susceptibility to colds, dyspnea, weight gain, decreased libido, dryness of the mouth, deafness, anorexia, and pancreatitis when epigastric pain or unexplained G.I. symptoms develop after prolonged administration. Jaundice, xanthopsia, paresthesia, photosensitization and necrotizing angiitis are possible. *Average Dosage:* One tablet daily with breakfast. *Availability:* Pink, single-scored tablets in bottles of 100 and 1000. (B)46-600-C

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Management-Comprehensive Treatment of Cystic Fibrosis*

LE ROY W. MATTHEWS, M.D.†
CARL F. DOERSHUK, M.D.†
Cleveland, Ohio

Cystic fibrosis has been defined as a generalized disease of the exocrine glands of the body involving the respiratory tract, the digestive and reproductive tract and the sweat glands, but recent tissue culture studies by Danes and Bearn[1] demonstrating the accumulation of metachromatic material in fibroblasts from patients with cystic fibrosis and their heterozygous parents (when grown in tissue culture) suggest that it is an even more generalized defect.

Truly successful treatment of this disease must await clearer definition of both the basic defects and the associated secondary abnormalities. In the meantime, our therapeutic efforts must be directed empirically against all the known manifestations of the disease, many of which are probably secondary to as yet unrecognized abnormalities. From what is known already, some of these abnormalities result from variable genetic make-up, but others are secondary to environmental factors, including exposure to infection, surgery, malnutrition, variations in therapy, and socioeconomic factors.

Treatment must be both individualized and comprehensive. All the manifestations of the disease as they appear in individual patients must be treated, and, where possible, the development of these manifestations should be prevented. A physician devoted to the practice of good preventive medicine can prevent or significantly delay many of the complications of cystic fibrosis such as malnutrition, fat-soluble vitamin deficiencies, intestinal obstruction due to fecal impaction, rectal prolapse, atelectasis, chronic obstructive pulmonary disease, and bronchiectasis. Because ninety percent of the morbidity and mortality associated with the disease results from secondary infection of the respiratory tract, therapy aimed at preventing such involvement markedly alters the course and the prognosis of the disease.[2]

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*Read at the Regional Continuation Course on Chronic Respiratory Diseases in Children and Adolescents at the University of Minnesota, Minneapolis, September 17, 1968.

†Babies and Children's Hospital, Case Western Reserve University School of Medicine, Cleveland, Ohio.

Pulmonary Changes

All of the changes produced in the lungs tend to be self perpetuating (Figure 1). The initial lesion is an accumulation of secretions in the smaller bronchi and bronchioles which either impairs or results from impairment of the normal mechanisms of pulmonary hygiene. The changes such as regional hypoxemia in the respiratory tract that result from this lesion probably, in themselves, further impair the mucociliary mechanism. The resulting stagnation of secretions in the respiratory tract then leads to secondary infection which, in turn, stimulates an increased production of secretions, the addition of exudative products such as deoxyribonucleic acid to the secretions, increased obstruction due to mucosal edema and further impairment of ciliary activity as a result of mucosal inflammation. Obviously, this results in a vicious cycle with obstruction leading to infection and infection leading to more obstruction and increased infection. To be effective, therapy must be aimed at either preventing or breaking this cycle before irreversible damage results.[3] If one waits until irreversible changes such as squamous cell metaplasia, bronchiectasis and pulmonary fibrosis appear, the course of the disease becomes more progressive despite all currently available therapy.

Cystic fibrosis is a diagnosis that strikes terror into the hearts of most parents and often results in severe guilt feelings and great anxiety. The knowledge that a thorough evaluation was made before arriving at the diagnosis and before prescribing therapy does much to help the parents accept both. The period of hospitalization then provides an opportunity to use intensively all indicated therapeutic measures to bring the disease under control and to evaluate the individual patient's response to each. Such evaluation is essential if one is to avoid producing iatrogenic disease. Much can also be done during this period to allay the natural fears of the older child. Infants and young children's fears usually parallel the anxiety state of the parents and must be treated through them. Patient acceptance of a comprehensive and, where possible, prophylactic treatment program is extremely important. Most children will accept the mist tent, aerosol treatments, postural drainage and medications quite readily from trained hospital personnel. Those who resist can be slowly brought to acceptance with much less emotional stress when this is done by individuals who are less emotionally

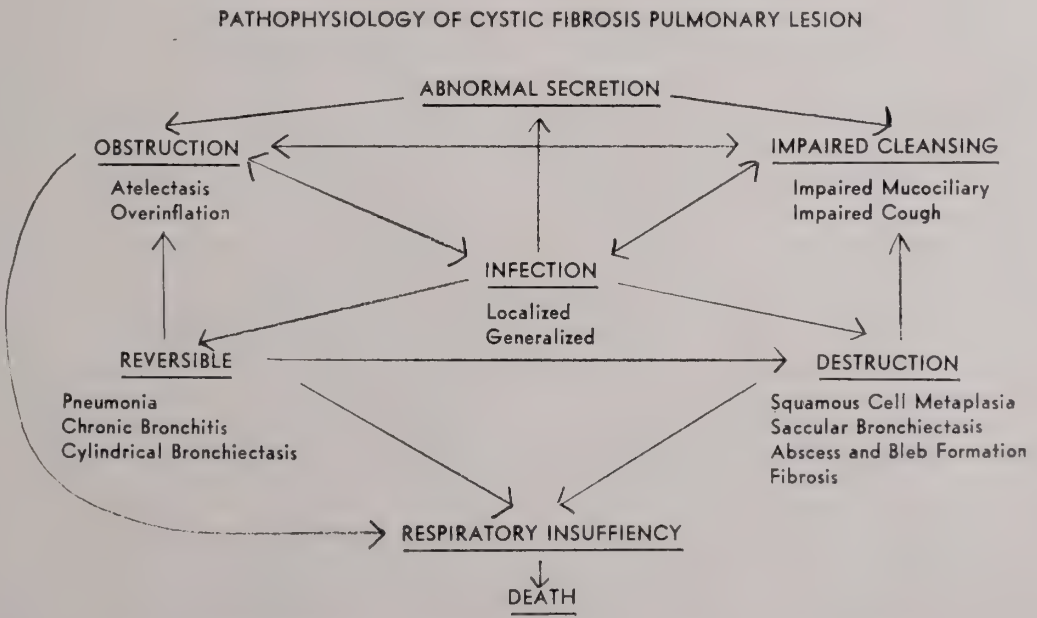
PATHOPHYSIOLOGY OF CYSTIC FIBROSIS PULMONARY LESION
ABNORMAL SECRETION
OBSTRUCTION
Atelectasis
Overinflation
IMPAIRED CLEANSING
Impaired Mucociliary
Impaired Cough
INFECTION
Localized
Generalized
REVERSIBLE
Pneumonia
Chronic Bronchitis
Cylindrical Bronchiectasis
DESTRUCTION
Squamous Cell Metaplasia
Saccular Bronchiectasis
Abscess and Bleb Formation
Fibrosis
RESPIRATORY INSUFFIENCY
DEATH

Fig. 1—Interrelationships in the pathophysiology of the cystic fibrosis pulmonary lesion.

involved with the child than the anxious, often guilt-burdened parents. Once this is accomplished, then the parents are brought into the treatment program and thoroughly instructed on their own children. Usually the child welcomes this change because he feels more secure in the hands of his parents. Only after the parents express confidence in their ability to carry out the therapy is the whole program transferred to the home.

Prevention of Progression

As with any chronic disease, if one is to be successful in preventing progression, it is essential that a close parent-patient-physician relationship be established. A thorough knowledge of what cystic fibrosis is, how it causes symptoms, what the symptoms mean, and how the treatment works will allay more fears than it produces and will greatly facilitate the establishment of an effective prophylactic home care program. To accomplish this, the physician must come down to the patient's and parents' level of understanding. He must use descriptive language. In talking about the normal mechanisms of pulmonary hygiene he must draw pictures, describe the normal mucus stream as a fast running mountain stream and that in the cystic fibrosis lung as a sluggish stream winding through a swamp. Bronchial obstruction can be compared to nasal obstruction with which everyone is familiar, coughing to nose blowing, the effects of neosynephrine in bronchi to its effects in the nose, and the lung to a balloon. Using this approach in a detailed fashion we have yet to see a family that could not understand the information presented, and we have had both parents and 12-year-old patients go home and deliver almost verbatim lectures to their local National Cystic Fibrosis Research Foundation chapters.

Inform the Child

A few families have attempted to keep the diagnosis from the child; such efforts have always been unsuccessful. These children then interpret the secrecy as ominous and live in silence with anxiety and fears of death that are often not justified by their condition. They become depressed and withdrawn or rebellious, but they usually do not reveal their knowledge to their parents. This situation deprives the child of very essential support and often leads to inadequate therapy. Every effort should be made to instruct the child at a level commensurate with his ability to understand. In discussing his condition it is usually advantageous to stress his good points and minimize his handicap. Many patients, especially teenagers, need subtle help in resisting the over-protective tendencies of their parents, in guiding their ambitions and in directing their activities into channels where the feedback will increase their sense of self importance and independence.

Family and Friends

Instruction of the patients, parents and older siblings or close relatives in the practical aspects of the therapeutic measures is extremely important, but it is equally vital that they understand how each measure works, what it accomplishes and why it is used. Certainly the knowledge that these measures are used prophylactically is essential both to decrease anxiety and to maintain the cooperation of the parents and the patients. It is also usually beneficial if the responsibility for long-term care is assumed by the physician, leaving the parents and patient only with the responsibility for day-to-day care.

Treatment

Prophylactic Therapy

Prophylactic therapy should include the measures aimed at assisting the normal mechanisms of pulmonary hygiene (aerosol and mist-tent therapy, postural drainage and physical activity), preventing viral pulmonary infections (measles and influenza immunizations), guarding against malnutrition and fat-soluble vitamin deficiencies, avoiding excessive sweating and the development of hyponatremia, and detecting pulmonary infection (frequent physician evaluation, bacteriologic and pulmonary function evaluations). Failure to control the gastrointestinal or sweat salt losses or to recognize the onset of diabetes or psychologic depression may have a marked effect on the pulmonary lesion and vice versa.

Clinically, cystic fibrosis is primarily a pulmonary disease and, as a result, the pulmonary lesion must be intensively treated. Most of these patients were found to have increased airway resistance, abnormal lung volumes and decreased arterial PO_2, indicating the presence of early pulmonary involvement. We have also demonstrated that treatment of these patients, with measures aimed at assisting the normal mechanisms of pulmonary hygiene in clearing their bronchial tubes, returns their lungs to more normal function. This is the chief reason we advocate the initiation of mist-tent therapy and the intermittent use of decongestant aerosols followed by postural drainage, as prophylactic measures. This probably results in over-treatment of a few patients, but there is no way currently available of identifying these few. It does not seem justifiable to sacrifice the majority to progressive pulmonary disease in order to avoid this over-treatment of a small minority.

Mist-Tent Therapy

Mist-tent therapy[4,5] is used to wet and thin the pulmonary secretions. In some patients propylene glycol may cause wheezing and evidence of bronchial irritation; in these instances an ultrasonic nebulizer used with half-strength normal saline provides an excellent fog, free of propylene glycol. To avoid any harmful effects mist-tent therapy should always be initiated and evaluated in the hospital before it is included in the home-care program. The jet-type nebulizer tents have been quite effective in most patients on prophylactic therapy and have the advantage of lower initial cost, ease of maintenance, and reliable operation. The ultrasonic nebulizer tents are more expensive, more difficult to maintain and less durable, but they are also more effective in the treatment of patients with significant chronic pulmonary involvement.

Aerosol Medication

Intermittent medication aerosol therapy is used to open up the respiratory tract, thus facilitating effective coughing and postural drainage. In general, 2 ml. of a solution containing nine parts 0.125% phenylephrine hydrochloride and one part USP propylene glycol are inhaled three to four times a day preceding postural drainage. Antibiotics should be added only when indicated. Depending on the size of the patient, 0.2 to 0.5 ml. of 1:200 solution of isoproterenol can be added to each aerosol, if indicated for bronchospasm.

Other medications occasionally used to treat the obstructive pulmonary manifestations include oral bronchodilators, and expectorants such as potassium iodide, hydriotic acid and iodinated glycerol. When the latter medications are used the patient should be closely observed for sensitivity reactions, goiter or hypothyroidism.

Postural Drainage Physiotherapy

Segmental postural drainage[6] with clapping and vibration of the chest provides effective drainage of bronchial secretions that have been thinned by mist-tent therapy, from the bronchial tree that has been opened by the aerosol decongestant and bronchodilator therapy. These measures complement each other and should be used together for maximum effects. In the hospital, postural drainage is performed three to four times daily following aerosol therapy. The duration must be adjusted to the tolerance of severely ill patients, but it should not be discontinued. Sometimes more frequent treatments for short periods of time are indicated. Patients with a pneumothorax, hemoptysis or cor pulmonale, and postoperative patients should be continued on intensive therapy since their survival depends on bringing their obstructive pulmonary disease under control. At home, prophylactic drainage of each segment is recommended twice daily. Localized disease or significant generalized involvement requires more intensive and longer treatment of the more involved areas. For all patients deep breathing and coughing are important parts of the postural drainage routine and should be encouraged in each position.

Physical Activity

Physical activity is another important aid in preventing the accumulation of secretions in the bronchial tree. Confinement to bed should be avoided even during hospitalization. Small infants, postoperative or severely ill patients should be turned and positioned frequently. For ambulatory patients, dancing, running, swimming, athletic activities and active play should be encouraged.

Management of Sequellae

Chronic Sinusitis

Patients with cystic fibrosis almost invariably develop chronic sinusitis; about 10% develop nasal polyps, and a significant number develop allergic asthma. The sinusitis should be treated with both topical and oral decongestant therapy; a few patients require sinus drainage.

Allergic Diseases

Local therapy is generally unsuccessful in the treatment of nasal polyps, but allergic desensitization therapy may decrease the rate and incidence of recurrence. When nasal obstruction occurs polypectomy is indicated. Asthma is a serious complication which must be thoroughly evaluated and intensively treated. Environmental and dietary allergens must be identified and eliminated if possible. Bronchodilators, by both aerosol and systemic routes, should be used, and also steroid therapy if indicated.

Obstructive Airway

In a small group of infants with cystic fibrosis who present with severe peripheral airway obstruction due to edema, congestion and bronchospasm, but without significant evidence of infection, steroid therapy may be life-saving. When intensive pulmonary therapy does not quickly initiate improvement in such infants, steroids in a dosage equivalent to 10-12 mg. per kilogram per day of cortisone may be extremely effective in breaking the vicious cycle. These infants probably do not have asthma since, with subsequent continuation of the usual therapeutic measures, the wheezing does not recur. All such patients should be watched carefully for evidence of pulmonary infection and treated vigorously with antibiotics if it appears.

Therapy of the Pulmonary Infection

Obviously, all of the previously mentioned therapy has been directed primarily at the accumulation of secretions and the obstructive lesion in the bronchial tree. This therapy was deliberately discussed first, because we believe it is more closely related to the basic defect in the respiratory tract and is essential for effective treatment of the secondary bacterial infection.

Identify Sensitivities

In cystic fibrosis, Staphylococcus aureus, Pseudomonas aeruginosa, Hemophilus influenzae, Proteus vulgaris, Escherichia coli or Klebsiella pneumoniae organisms[7,8] are noted for their tendency to cause low-grade chronic infection and for their tendency to become resistant to the more commonly used antibiotics. In patients with early pulmonary involvement and with staphylococcal or hemophilus influenza infections complete clearing of the infection should be the goal and may require two to 12 weeks of intensive antibiotic therapy. During this period the agent or agents used should be changed to match the changing bacterial flora and sensitivities, which should be reevaluated at weekly intervals. If the patient does not show a definite response to such therapy the presence of L-forms of staphylococci[9] should be suspected and treatment with lincomycin or erythromycin prescribed.

Pseudomonas Organisms

Early in the course of cystic fibrosis the Pseudomonas organisms isolated are usually sensitive in-vitro to tetracycline, chloroamphenicol, sulfisoxasole, carbenicillin, streptomycin, colistin, polymyxin, and neomycin. Intensive treatment with these drugs may eradicate the organism in patients with little or no irreversible damage in their bronchial tree, but elimination is rarely if ever possible in patients with more advanced disease even though marked clinical improvement may occur. In some patients continuous infestation with Pseudomonas does not appear to further damage the lungs, but in most it is pathogenic and produces progressive damage. Rapid progression in such patients may occur if antibiotic therapy is withheld. In patients with advanced pulmonary disease continuous high-dosage antibiotic therapy is often necessary to maintain control of the infection. In many patients the presence of two or three varieties of pathogenic organisms with differing antibiotic susceptibility requires the use of more than one antibiotic. As the disease advances the predominant flora becomes Pseudomonas organisms sensitive only to polymyxin, colistin, gentamicin and carbenicillin. The latter is still available only for investigational use. Carbenicillin is a synthetic penicillin which can be given parenterally in high dosage without producing toxic effects. We have now used this antibiotic on 42 patients with advanced disease, most of whom have shown significant clinical and pulmonary function test improvement but failure to clear the Pseudomonas. A non-toxic truly effective antibiotic for the treatment of Pseudomonas bronchial infections remains the greatest need in therapy.

Follow-up Treatment

After the initial period of intensive hospital treatment further antibiotic therapy depends on follow-up outpatient evaluations at four to six-week intervals. Bacterial pulmonary infection may develop despite the most intensive efforts to maintain good pulmonary hygiene. The primary purpose of the follow-up evaluations is the early detection of recurrence of either the obstruction or the infection.

Detect Early Signs of Infection

To accomplish this a careful interval history covering the patient's general activity, any respiratory or pulmonary symptoms, and the effectiveness of therapy should be obtained. Special attention should be paid to the minimal symptoms and signs of early, low-grade infection including fatigue, irritability, decreased appetite and exercise tolerance, increased cough or development of a night cough, signs of air-trapping, rales, wheezing, an increase in respiratory rate and failure to gain weight or actual weight loss. Fever and toxicity are rarely encountered. When such evidence of infection is found and the routinely obtained throat or sputum culture reveals a significant pathogen, full-dosage antibiotic therapy is prescribed for a minimum of two weeks and up to three or four weeks or longer, if necessary. In those patients who have no chronic pulmonary symptoms and who have only normal flora on culture no antibiotic therapy should be employed. Resistant Pseudomonas infections may respond to high-dosage tetracycline (100 mg/kilogram) even when in-vitro antibiotic sensitivity studies indicate resistance, but they may also require repeated hospitalization for parenteral colistin, gentamicin or carbenicillin therapy.

Pancreatic Deficiency

Comprehensive therapy requires attention to the pancreatic deficiency found in over 85% of patients with cystic fibrosis. Treatment is aimed at providing an adequate caloric intake. Small infants may require up to 200 calories per kilogram per day. A fat-free diet should be avoided in infants under one year of age since essential fatty acids should not be excluded during this period of rapid growth. Solid foods should be added early. The older child should be kept on a high protein diet with fat restricted according to tolerance. Rigid dietary control is not necessary, but in many cases excessively fatty foods should be avoided. In some patients high-calorie snacks including a preparation containing medium chain triglycerides may be helpful.

Therapy for Deficiency of Digestive Enzyme

In the patients with a demonstrable deficiency of pancreatic digestive enzyme function, pancreatin therapy results in improved digestion and absorption.

Pancreatin Preparations

Several satisfactory pancreatin preparations (one to three capsules or one to two packets per feeding), Viokase (one half to two tsp. or two to 10 tablets per feeding) or Panteric Granules (one half to one tsp. or two to six capsules per feeding) is usually effective. We prefer Cotazym because it is generally effective in a smaller dosage, is better accepted by the patient and produces less odor in flatus, urine and stools. This is extremely important to the child who is embarrassed by the teacher calling recess every time he passes flatus or the comments of his classmates after he uses the rest-room facilities.

Bile Salts

Selected patients show further improvement in the degree of steatorrhea and in stool consistency when bile salts are added in the form of Convertin, Cotazyn B or Accelerase (one to two tablets or capsules per meal). A few patients and/or parents manifest an allergic response to pancreatin. Such patients may be treated with Papase. Infants with cystic fibrosis may be erroneously diagnosed as having asthma and treated with soybean formulas. If meat or some other high-quality protein is not added to the diet such infants may present with hypoalbuminemia and gross edema.

Vitamins and Salt

To prevent vitamin A, D, E, and K deficiencies from influencing the course of the disease we routinely prescribe water-soluble multivitamin preparations in twice the usual daily dosage. Because autopsy studies of patients with cystic fibrosis have revealed ceroid* pigment in the smooth muscle of the intestinal tract and degenerative changes in skeletal muscle and because clinical studies of vitamin E have revealed very high requirements in these patients, Aquasol E is prescribed in a dosage of 50 mg. per day under two years of age and 100 mg. per day thereafter.

Because excessive amounts of sodium and chloride are lost in the sweat of cystic fibrosis patients during hot weather, febrile illnesses and strenuous exertion, sodium chloride in doses of one to five grams per day is prescribed.

Complications

Other complications of cystic fibrosis must be constantly watched for. Acute intestinal obstruction or meconium ileus equivalent, biliary cirrhosis with bleeding from esophageal varices, ascites or hypersplenism, diabetes and growth failure or delayed puberty all require early detection and treatment. Finally, psychological problems are frequently encountered. Every effort should be made to recognize such problems early and to deal with them, utilizing all available community resources including social workers, psychiatric social workers, psychologists and, if necessary, psychiatrists. Vocational rehabilitation counselors are often very helpful in dealing with teenagers and young adults.

Clinical Studies

For the past 12 years we have attempted to provide a comprehensive and where possible prophylactic treatment program for all of our patients with cystic fibrosis. During the 10 years from July 1, 1957, through June 30, 1967, 404 patients with cystic fibrosis were admitted to this program (Table 1) for a total of 1677 years of follow-up care.

Thirty-seven of these patients died during the 10-year period, yielding a crude mortality rate of 2.2%.

Evaluation of Prophylactic Program

Several years ago we published our results on five years' experience with this treatment program on the first 98 consecutive patients seen.[3]

TABLE I
Ten Year Mortality

	Followed	Consultation
Number of patients seen	404	50
Patient years of follow-up	1677	
Number of deaths	37	7
Mortality rate/year of follow-up	2.2%	

All of these patients have been evaluated at frequent intervals using modified Shwachman and Kulczycki[10] criteria, grading them from 0 to 25 points for each of the four categories: (1) General Activity, (2) Physical Examination and Cough History, (3) Growth and Nutrition, and (4) X-ray Examination of the Chest (Figure 2).

0-25	**General Activity:** School attendance, play activity, exercise tolerance, personality.
0-25	**Physical Examination and Cough:** nature and severity of cough, chest findings, clubbing and cyanosis, pulse and resp. rate.
0-25	**Nutrition:** Weight and height percentile, dietary and stool history, muscle mass and strength.
0-25	**X-ray Findings:** Emphysema, atelectasis, fibrosis, bronchial markings, cavitation, cyst formation, infiltration.

Fig. 2—Clinical evaluation criteria used for grading all patients initially and at six-month intervals. Scores of 0-25 points were assigned for each of the four categories, a perfect score being 100 points.

Early and Reversible Involvement

These patients were divided into two groups using the relatively objective x-ray score. The 49 patients who presented with an x-ray score of 19 or more points of a possible 25 or who responded to therapy and subsequently attained such a score at any time during the follow-up period were considered to have early and reversible pulmonary involvement and to be on prophylactic therapy. Objective data collected on these patients, including growth and weight changes, morbidity and mortality, and pulmonary function studies, showed good correlation with the clinical evaluations. No evidence of significant progression of the pulmonary lesion was observed by any criteria for the prophylactically treated group. Indeed, mean pulmonary function test results for these patients were well within the range of normal values even at the end of the average four-and-a-half-year-follow-up period at an average age of seven years. No deaths occurred in this group. This study gave great impetus to the concept that early diagnosis and a prophylactic approach to treatment are essential for control of the pulmonary lesion of cystic fibrosis.

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*See Test Your Word Score Page 1401.

The remaining 49 patients never attained an x-ray score over 18 points and were considered to have irreversibly damaged lungs requiring therapeutic management. The overall mortality rate of less than 2% per year of follow-up with no deaths under six years of age indicated the effectiveness of the therapeutic program.

Follow-up

These 98 patients were reevaluated as of June 30, 1967, at the end of 10 years' experience with the treatment program. Only three of the 98 had been lost to follow-up and one other had transferred to another center for the previous two years. Fifteen had died. The remaining 79 patients continued on therapy and returned regularly for follow-up evaluations.

The clinical parameters, physical examination, chest x-ray and total score for the 49 patients who achieved a chest x-ray score of 19 or more points at some time during follow-up and were thus considered to be on prophylactic care, were evaluated for the period from one year on treatment to June, 1967. The one-year score was selected because maximum improvement on therapy is seen in most cases by then. The evaluation was aimed at determining the effectiveness of therapy in preventing progression after maximum benefit was obtained. Three of the original 49 patients in this group were lost to follow-up after 37 to 54 months. The total mean period of therapy for the remaining 46 patients was eight years, 10 months (range six years four months to 10 years). The mean initial physical examination score, which was 16 points, rose to 21 points at one year and remained at 21 points at the end of the follow-up period. The mean initial score for x-ray was 17 points, rose to 21 points after one year and remained at 20 points in follow-up. Only two patients deteriorated by more than four points. The mean initial total score which was 66 points rose to 87 points at one year and remained at 86 over the follow-up period. Six patients were improved by more than five points, 28 remained unchanged (± 5 points) and only 12 showed deterioration of more than five points from their one-year to most recent score. Five of these patients showed decreases of more than 10 points.

For the 49 patients whose pulmonary involvement was severe enough (x-ray score never greater than 18 points) to require therapeutic management, the mean period of follow-up was six years, eight months (range two years to 10 years). This period was shorter because of the deaths which occurred in this group. Their mean initial score for physical examination, which was 11 points, improved to 16 points after one year and fell to 12 points by June 30, 1967. For this group the mean initial score for x-ray, which was eight points, improved only to 10 points and fell again to eight points. Their mean total initial score, which was only 48 points, rose to 63 after one year and then fell to 53 points at the end of the ten-year period. Over 50% (28 of 49) were worse by more than five points.

These clinical evaluation studies revealed a significant difference between the two groups of patients. Those started on therapy before irreversible damage to their lungs had occurred showed little or no tendency toward progression of their pulmonary lesion. In contrast, significant progression was seen when the same or more intensive therapy was provided after significant pulmonary involvement had occurred.

Mortality

There was only one death in the group of patients treated prophylactically. She was a patient who was severely ill until diagnosed at age two years, who improved dramatically on therapy for five years, then failed gradually and died of pulmonary complications at eight and a half. In contrast, there were 14 deaths in the patients requiring continuous therapy. The mean initial x-ray score for these 14 patients was only seven points, and only one was above 13 points.

The more objective pulmonary function test data (Table 2) substantiates the results of the clinical evaluations. Since many patients were too young for accurate testing when first seen, the results of tests obtained after 12 to 18 months of treatment or when the patient was age five to six years were used and compared to the previous test results. For the patients who died, the last test prior to severe deterioration was used.

Conclusions

This data lends further support to the hypothesis that effective therapy is possible only when the diagnosis is made before significant irreversible damage has occurred in the lungs and when currently available therapeutic measures are used to prevent the development of chronic infection and associated destructive changes. Life table data offers additional support for this concept and also shows the overall value of comprehensive therapy.[11]

TABLE 2

Pulmonary Function Test Results

Chest x-ray group	19 to 25		0 to 18	
Number of patients	46		39	
Mean follow-up	8 yrs. 10 mo.		6 yrs. 10 mo.	
	1 year	Last	1 year	Last
Vital capacity (of predicted)	100%	99%	88%	72%
Functional residual capacity (of predicted)	99%	106%	118%	139%
Residual volume (of predicted)	100%	111%	145%	229%
RV/TLC ratio	.27	.28	.37	.49
Maximal breathing capacity (of predicted)	94%	98%	80%	75%
Forced expiratory volume, 1″	77%	68%	66%	51%

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*James Harvey Young: The Medical Messiahs, 1967.

Bachelors

A bachelor gets tangled up with a lot of women in order to avoid getting tied up to one.—Helen Rowland

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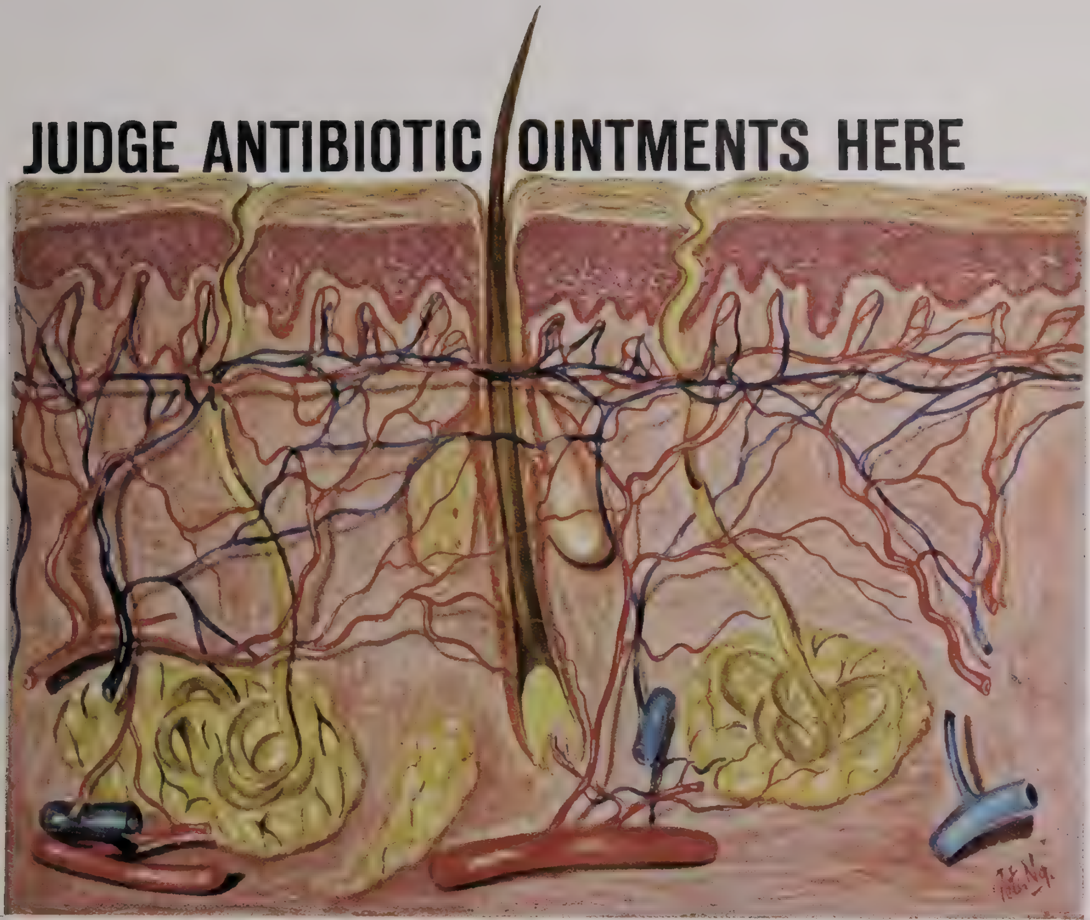

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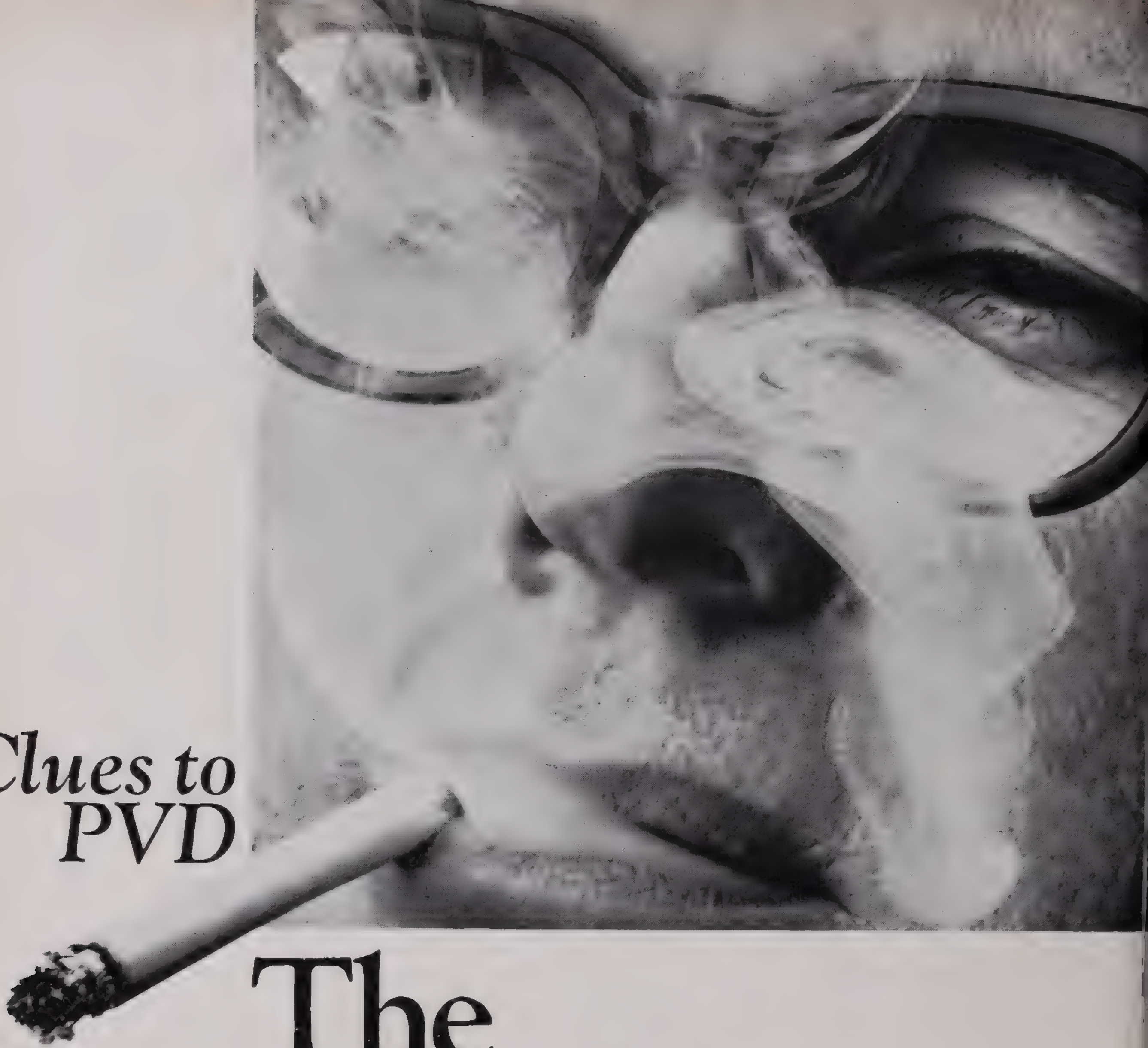

Clues to PVD

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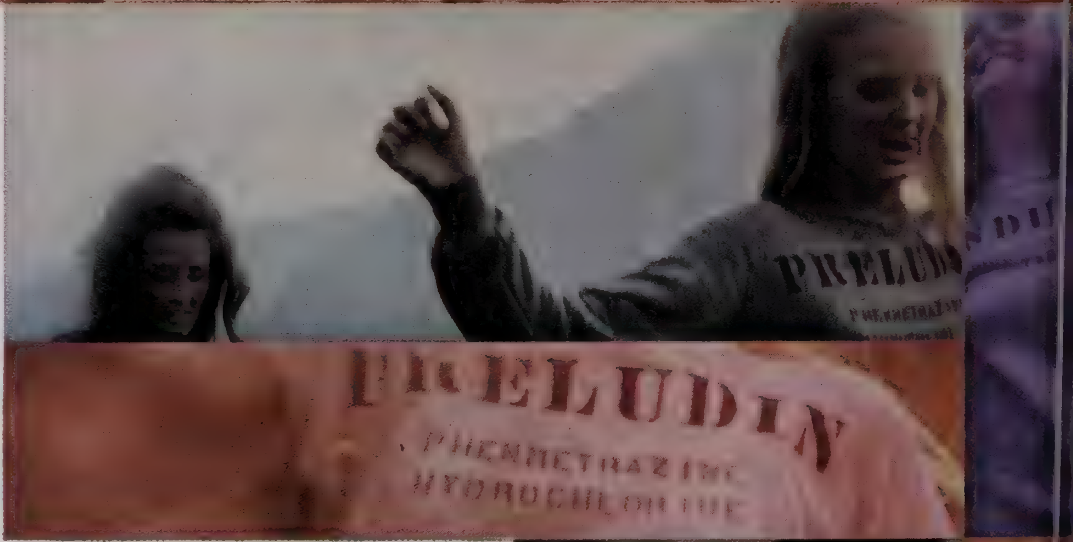

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Meetings and Announcements

American Medical Writers Association

The North Central Chapter of the American Medical Writers Association meeting November 1, 1969, 1:00 P.M., Judd Hall, Mayo Clinic, Rochester, Minnesota. Social hour and dinner, New Sheraton, Rochester, 7:30 P.M. All doctors interested in medical writing are welcome, wives included.

University of Minnesota

Fourth Annual Symposium on Kidney Disease

The University of Minnesota will conduct a course for the Upper Midwest Chapter of the National Kidney Foundation on September 20, 1969. Half of the program will be devoted to urinary tract infection and the other half to a discussion of transplantation and its implications for the local practitioners.

Hypnosis in Medicine

The University of Minnesota will conduct a course in Hypnosis in Medicine to be offered on September 25-27, 1969. The course will be co-sponsored by the American Society of Clinical Hypnosis Education and Research Foundation and the Minneapolis Clinic. The course is designed to familiarize practicing physicians with the uses of hypnosis in clinical medicine. For further information on the above courses contact: Lee D. Stauffer, College of Medical Sciences, Box 193, Mayo Building, University of Minnesota, Minneapolis 55455.

Mayo Clinic Clinical Reviews

A program of lectures and discussions on problems of general interest in medicine and surgery will be held at the Mayo Clinic and Mayo Foundation, Rochester, Minnesota. Identical sessions are offered on November 3, 4, 5, 1969 and November 10, 11, 12, 1969.

This program is acceptable for credit by the American Academy of General Practice and the College of Family Physicians of Canada. The registration fee for this program is $20.

The number of physicians who can be accommodated is necessarily limited. For this reason identical programs will be offered two successive weeks. The program will be presented first on November 3, 4, 5, and repeated on November 10, 11, 12. Those wishing to attend should communicate with M. G. Brataas, Mayo Clinic, Rochester, Minnesota 55901, indicating which session they would prefer to attend.

Stroke Conference

September 19-20, Pick-Nicollet Hotel, Minneapolis, Minnesota. Conference—sponsored by The American Rehabilitation Foundation. Sessions include measurements of improvement in completed stroke, rehabilitative predictors in completed stroke, environmental correlates of differential outcomes, and implications for future research. Fee: $20; registration open to all disciplines. Contact: Dr. Thomas P. Anderson, 1800 Chicago Avenue, Minneapolis 55404.

Southern Minnesota Medical Association Meeting

Southern Minnesota Medical Association Meeting in Albert Lea, Minnesota, September 13, 1969, Inn Towne Motel (Heritage Hall). For details contact Dr. John J. Eustermann, Mankato Clinic or Ethel McClane, 1726 No. 4th St., Mankato.

Pulmonary Complications of Cystic Fibrosis[*]

HARRY SHWACHMAN, M.D.[†]
DOUGLAS S. HOLSCLAW, M.D.[†]
Boston, Massachusetts

THE CHIEF CAUSE of death in cystic fibrosis remains the pulmonary failure that results from the progression of the pulmonary lesion. We believe it is the rare patient with cystic fibrosis who escapes involvement; however, there are a small number who survive for many years with mild disease.

The pathogenesis of the pulmonary lesion in cystic fibrosis has been described (Figure 1). This is not a step-by-step sequence involving the entire lung at the same time; rather each one of these various steps is occurring in many different locations throughout the lung at any given time. This is further modified by varying degrees of severity in any one individual. Other more subtle changes occur, including metaplasia of the normal columnar ciliated epithelium of the bronchus into mucus-producing cells, which results in the increased elaboration of the abnormally viscous mucus and interrupts the usual upward flow of secretions secondary to loss of ciliated cells. In addition, infection results in focal obliteration of other ciliated cells and increases mucus production.

We shall now consider separately some of the pulmonary complications that may occur.

Air Trapping and Emphysema

Many factors combine to cause this, such as the ball valve action of mucus which partially blocks a bronchus, mucosal edema secondary to inflammation, bronchospasm on an irritative or allergic basis and restriction in the mechanics of ventilation because of the fibrosis and scarring that have taken place. At times, this emphysema can assume alarming proportions (Figure 2), with the A-P diameter of the chest being greater than the lateral. Although usually a slow insidious process, at times there may be rather acute changes in the chest configuration, especially in the infant. The residual volume of the lung increases, although the total lung capacity may not be increased due to lack of aeration of other areas of the lung.[1] The end result is a fixed, overdistended, restrictive chest which reduces the effectiveness of the cough so vitally important to these patients.

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[*] This work was supported in part by a Grant from the National Cystic Fibrosis Research Foundation.

Read at the Regional Continuation Course on Chronic Respiratory Diseases in Children and Adolescents at the University of Minnesota, Minneapolis, September 17, 1968.

[†] From the Division of Clinical Laboratories and the Department of Medicine, Children's Hospital Medical Center and Department of Pediatrics, Harvard Medical School, Boston, Massachusetts.

Bleb-Bullae-Pneumothorax

Another extension of chronic air trapping is the formation of subpleural blebs and bullae formation, a variable degree of which can be seen on the surface of the lungs, especially at the apices. At times these bullae can reach massive proportions (Figure 3). Considering the frequency with which these are found and the size to which some of them may grow, it is remarkable that so few rupture under the stress of forceful paroxysms of coughing. Spontaneous pneumothorax is becoming a considerable problem, especially in young adults with cystic fibrosis.[2] We have now encountered 88 episodes of pneumothorax in 46 different patients (Table 1) in our clinic over the past 18 years. Approximately 2,000 patients with cystic fibrosis were observed during this period. The right and left sides were involved almost equally and

TABLE 1

Pneumothorax in Cystic Fibrosis

1. 88 episodes in 46 patients
2. 34 males: 12 females
3. Right 38; left 42; bilateral 8
4. 42/88 (45%) recurrences
5. Average age at onset 14-5/12 years
6. Average clinical score 49 (moderate)

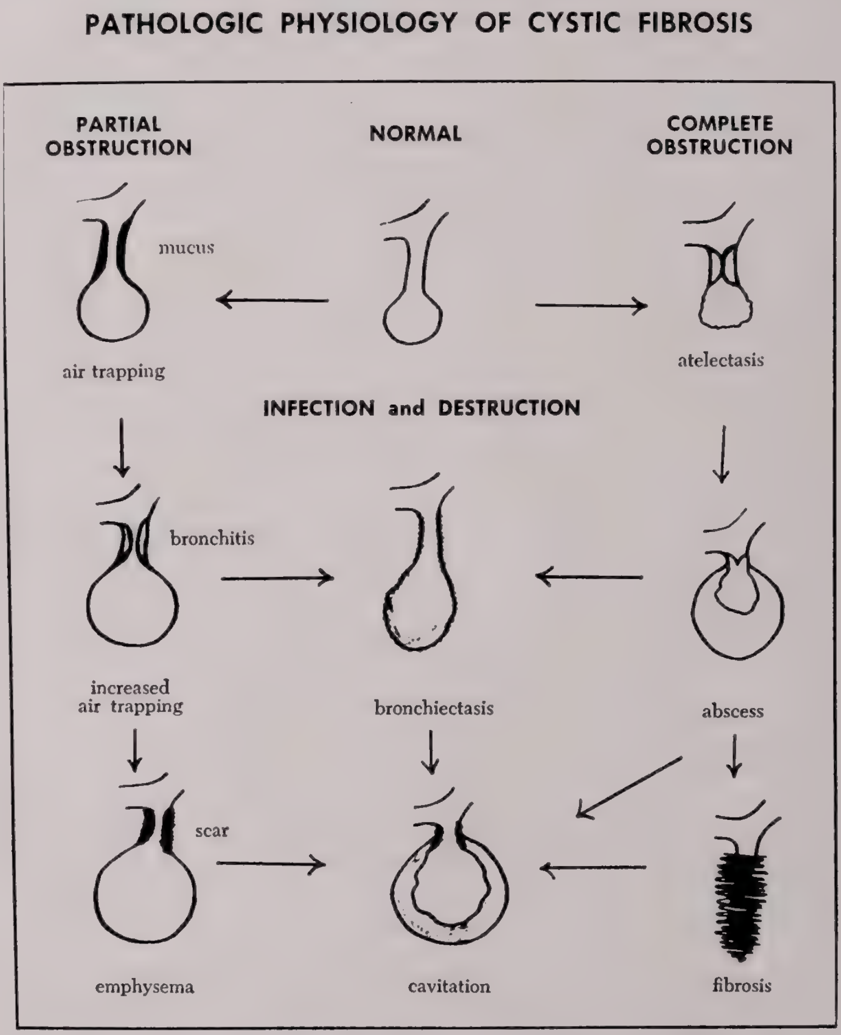
PATHOLOGIC PHYSIOLOGY OF CYSTIC FIBROSIS

Fig. 1—Sequence of progression of the pulmonary lesion. Diagram courtesy of the National Cystic Fibrosis Research Foundation.

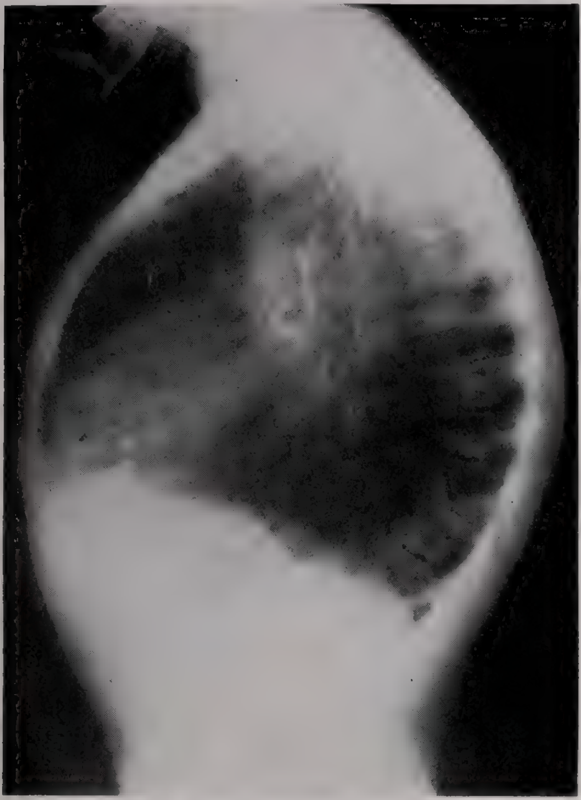

Fig. 2—Lateral chest film of a 13-year-old girl showing marked increase in anterior-posterior diameter and severe air trapping.

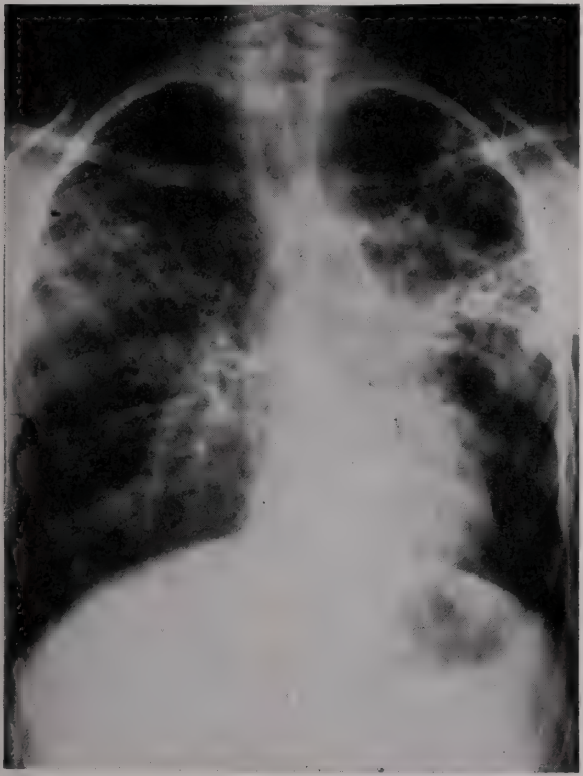

Fig. 3—Multiple large bullae have formed at both apices, compressing adjacent lung parenchyma.

there were eight instances of simultaneous bilateral episodes. The extent of the pneumothorax ranged from a minimal asymptomatic accumulation of pleural air to total collapse of a lung (Figure 4) at times with evidence of tension. At the time of the first episode of pneumothorax, the average age was 14 years and five months. Forty-two of the episodes were recurrences in 21 (45%) of the patients; half of the recurrences took place in the opposite hemithorax from the original. Most of the patients had moderate to severe pulmonary involvement prior to the initial episode. No specific precipitating factor could be identified. Some occurred while at rest or asleep; some while coughing; some with exercise; two with changes in altitude, and four related to the use of intermittent positive breathing apparatus. The majority of the patients (two thirds) were treated by tube thoracostomy.

There was a significant mortality associated with a pneumothorax (Table 2). Fifteen patients expired while hospitalized for a pneumothorax, or during a hospitalization in which a pneumothorax occurred. Seventeen patients died at a later date without signs of a pneumothorax, and 14 are currently alive. The average

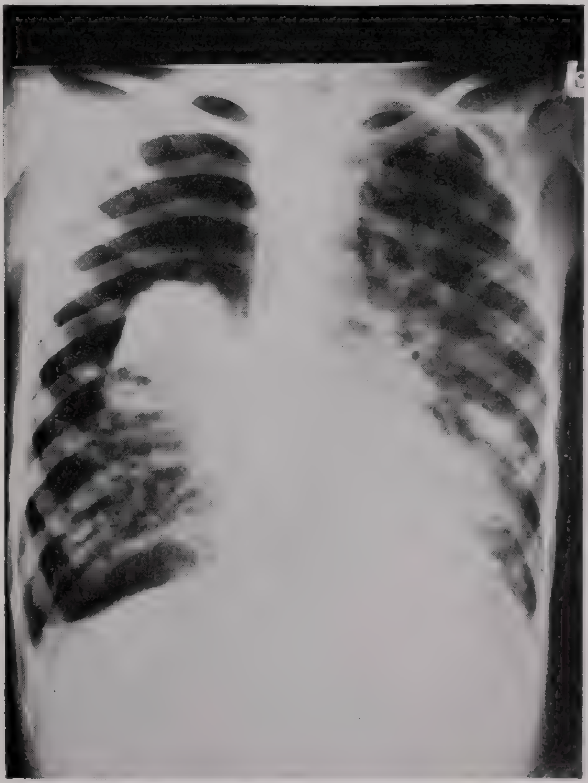

Fig. 4—Large right pneumothorax in a 12-year-old boy with advanced cystic fibrosis.

duration of time from the initial episode to death in 32 patients was 16 months.

On occasion pneumomediastinum will occur with or without a pneumothorax, and can spread as subcutaneous emphysema.

TABLE 2

Mortality of Pneumothorax—46 Patients

1. Expired while hospitalized for pneumothorax	15	
a) Pre-terminal event		2
b) Pneumothorax still present at death		12
c) Pneumothorax resolved at death		1
2. Expired at a later date without pneumothorax	17	
3. Currently living	14	

Lobar Atelectasis

A more complete or advanced form of mucus plugging results in lobar atelectasis. In young infants this commonly occurs in the right upper (Figure 5) or right middle lobe, although all segments may be involved.[3] A vigorous attempt should be made to re-expand the collapsed lobe or segment since the certain end result will otherwise be bronchiectasis and abscess formation. Atelectasis may occur following measles, pertussis or other infections, a fact which supports the need for early and complete prophylactic immunization against such conditions.

Atelectasis can involve an entire lung as well as a single lobe. In older patients this usually takes the form of a gradual collapse in a severely diseased lung over a period of several months (Figure 6). Large A-V shunts may develop so that the lung tissue is poorly perfused as well as poorly ventilated. If feasible, pneumonectomy should be performed.

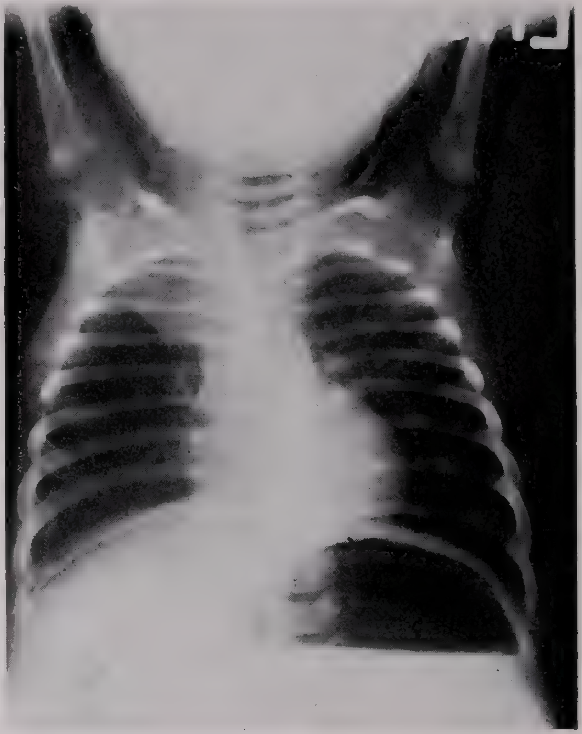

Fig. 5—Right upper lobe atelectasis in an infant, age six months, which was present when the patient was first seen and the diagnosis made. This collapse did not require resection.

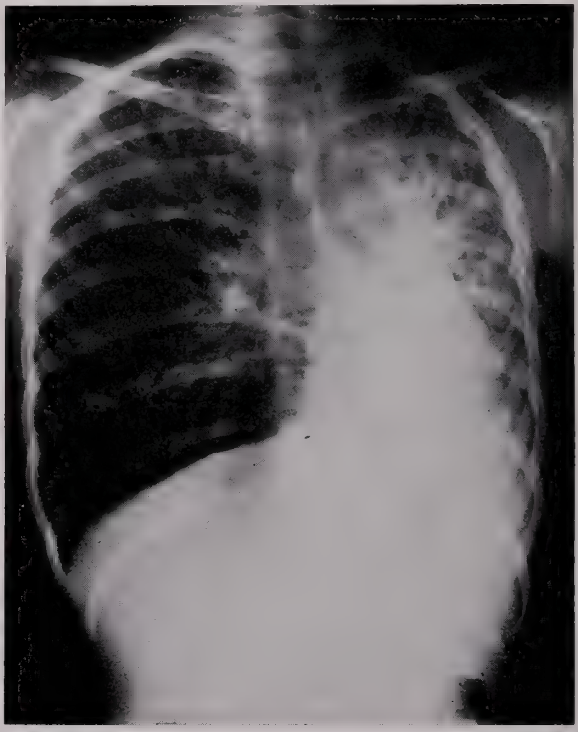

Fig. 6—Almost total collapse of the left lung with herniation of the right lung across the mediastinum. The collapse had gradually occurred over a two-year interval. Pneumonectomy followed.

Bronchiectasis

This takes place in collapsed areas of lung as well as in local areas when bacterial invasion and destruction of the bronchial wall have occurred. Bronchitis and stagnation of the accompanying secretions and exudate are two essential factors in the development of bronchiectasis. Characteristically, the bronchiectasis is multifocal and distributed throughout all lung fields. This is seen quite frequently in the upper lobes in contrast to the predominantly lower lobe distribution which is seen in the bronchiectasis which occurs in non-cystic fibrosis patients.[4] By x-ray, all anatomical variants of bronchiectasis are present (Figure 7): saccular, fusiform, or cylindrical. This widespread dis-

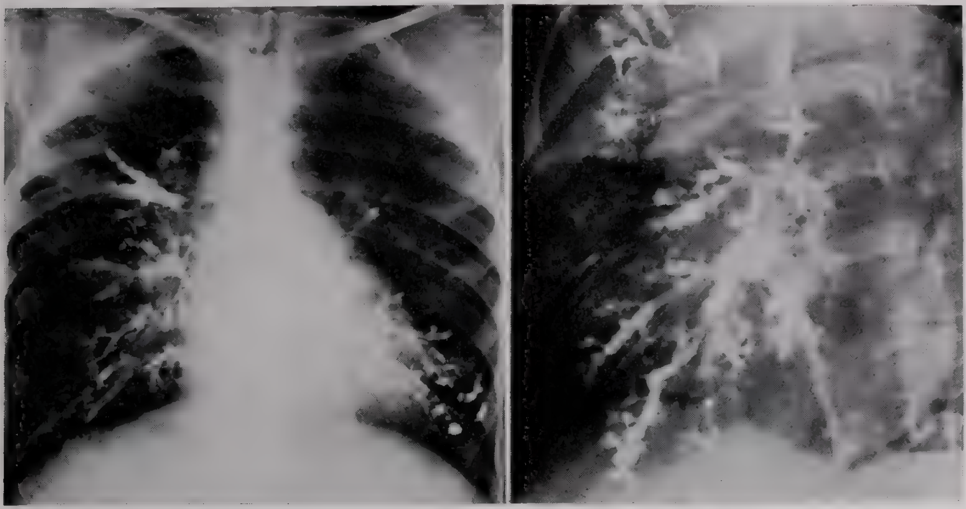

Fig. 7—Bronchograms revealing the multiple and widespread areas of involvement by bronchiectasis in a 14-year-old male.

tribution makes surgical resection impractical except for those cases where the disease is localized. When possible, surgical resection should be attempted[5] since the profuse exudate and secretions intensify the disease involving the remainder of the lung.

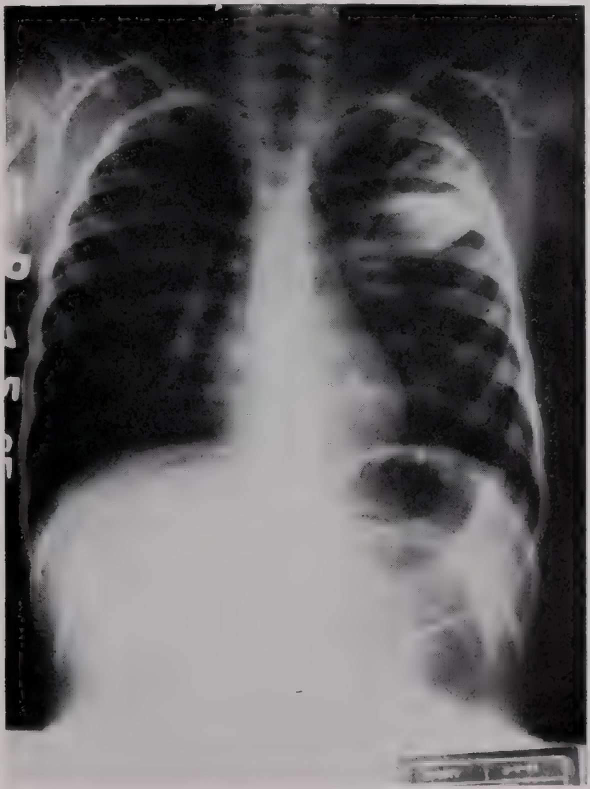

Fig. 8—Large left upper lobe abscess cavity with an air-fluid level. Note the relative absence of disease in the remaining lung fields. Treated by resection.

Hemoptysis

A direct consequence of the bronchial wall destruction associated with bronchiectasis is erosion of the surrounding bronchial and pulmonary arteries, resulting in massive hemoptysis. This complication is becoming increasingly more frequent, particularly in older patients with cystic fibrosis[6] (Table 3). The first blood-streaking in the sputum occurred at a mean age of 15 years, and the mean age of the initial massive hemoptysis was 18 years. In six patients the bleeding episode was the terminal event, death occurring immediately in four patients and within two days in another two. The cause of death was either immediate exsanguination or asphyxiation by the aspirated bronchial secretions. In all, 11 of the 16 patients had died within six months of their initial hemorrhage, indicating the severity of this complication and the poor prognosis which it carries. No particular precipitating factor could be identified, nor could any part of the pulmonary treatment regimen that they were receiving be incriminated. Over half the episodes, however, were associated with a pulmonary exacerbation. In all cases, the invading organisms were the Staphylococcus and Pseudomonas.

Routine chest films, bronchograms and bronchoscopy are of little help in localizing the site of the bleeding. Frequently, the patient is able to localize the site subjectively by a sense of warmth, or a bubbling, gurgling sensation a few seconds prior to the bleeding. At present, our only treatment has been limited to replacement of blood volume and symptomatic measures including vitamin K intravenously. In view of the serious prognosis, however, if the patient can be stabilized and a fair assessment of his pulmonary reserve made, perhaps surgical resection would be the desirable form of definitive therapy.

TABLE 3

Massive Hemoptysis in Cystic Fibrosis

1. 25 episodes in 16 patients
2. Average age onset blood-streaking 15 years
3. Average initial massive bleeding 18 years
4. 11/16 died in six months after initial bleeding
5. 13/25 associated with pulmonary exacerbation

Abscess

Although small abscesses very commonly occur in cystic fibrosis, large cavitary abscesses are rare. As a result of incomplete resolution of a large area of bronchopneumonic consolidation or by extension of the bronchiectatic process, on occasion a large pulmonary abscess will form. For some unexplained reason, three patients presented with large abscesses measuring between 30 to 40 millimeters with fluid levels during the summer of 1966. We had not seen this particular type of lesion prior to that time. These three required surgical resection. Two additional cases seen since then have responded to medical management. There may be an unexplained tendency for these large abscess cavities to recur in the same patient but in a different area. These patients had either normal or elevated gamma globulin levels. Our treatment has been massive and prolonged antibiotic therapy followed by surgical resection if resolution does not occur.

Fungal Abscess and Overgrowth

Related to localization and abscess formation is the rare patient with cystic fibrosis who develops a fungal mycetoma. This is most commonly due to *Aspergillus; Candida* and *Actinomyces* are seldom the etiologic agent. The

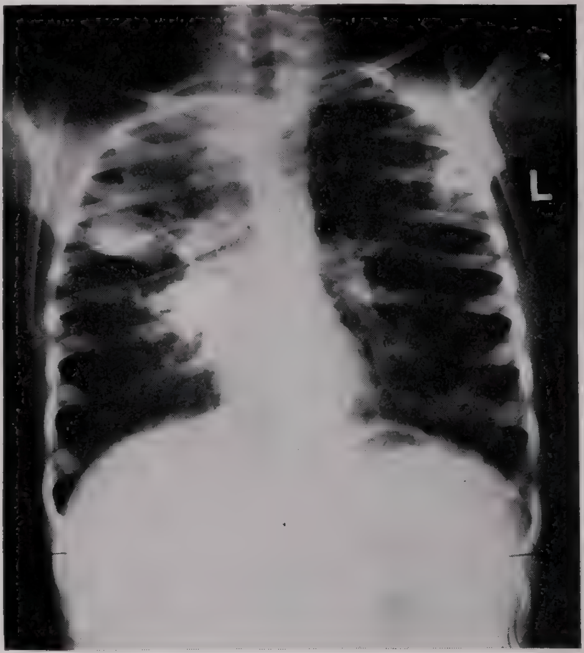

Fig. 9.—Circumscribed right upper lobe aspergilloma in a 14-year-old boy. Note the apical pleural cap. *Aspergillus* isolated repeatedly from the sputum.

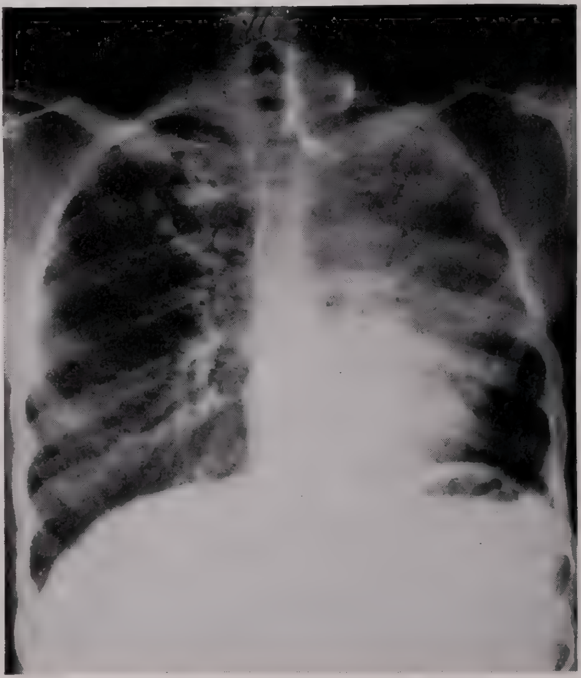

Fig. 10—Acute, hazy, diffuse left lung infiltrate in a 19-year-old boy. Eosinophiles of 28%. Positive sputum culture for *Aspergillus*.

Aspergillus may become localized as an aspergilloma (Figure 9) or can take a disseminated form as an acute infection, aspergillosis (Figure 10). There is a marked increase in the number of eosinophiles in the peripheral blood with fever and copious sputum production. In our cystic fibrosis clinic, some 31% of patients will have a serum-precipitating antibody titre against *Aspergillus* antigen, but very few at any one time will have *Aspergillus* cultured from their sputum.[7]

Botryomycosis

This is a rare and poorly understood chronic granulomatous process which bears a superficial resemblance to actinomycosis. The most common site is in the lungs, but the lesion may spread to adjacent structures. The clinical diagnosis is difficult unless drainage sinuses appear, and is usually made by pathological examination either on resected specimens or at postmortem. Fungal cultures are negative, but there is a constant finding of the bacteria *Staphylococcus aureus* or *Pseudomonas aeruginosa*. We have encountered this in seven patients, only two of whom are still living. This condition is an exception to the unique ability of the patient with cystic fibrosis in general to localize infection and prevent dissemination.

Empyema

Considering the 80-90% prevalence of

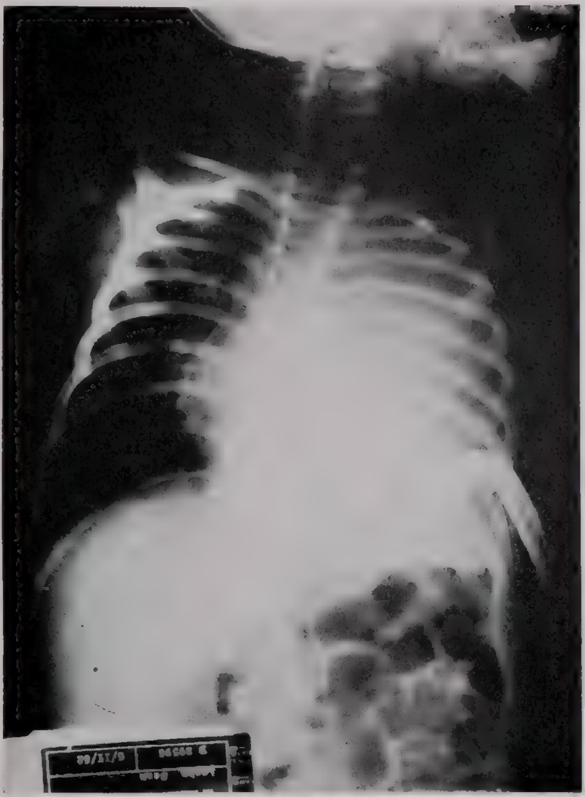

Fig. 11—Six-month-old boy with a massive left pleural effusion being treated by tube drainage. Has no localized sequellae now at age eight years.

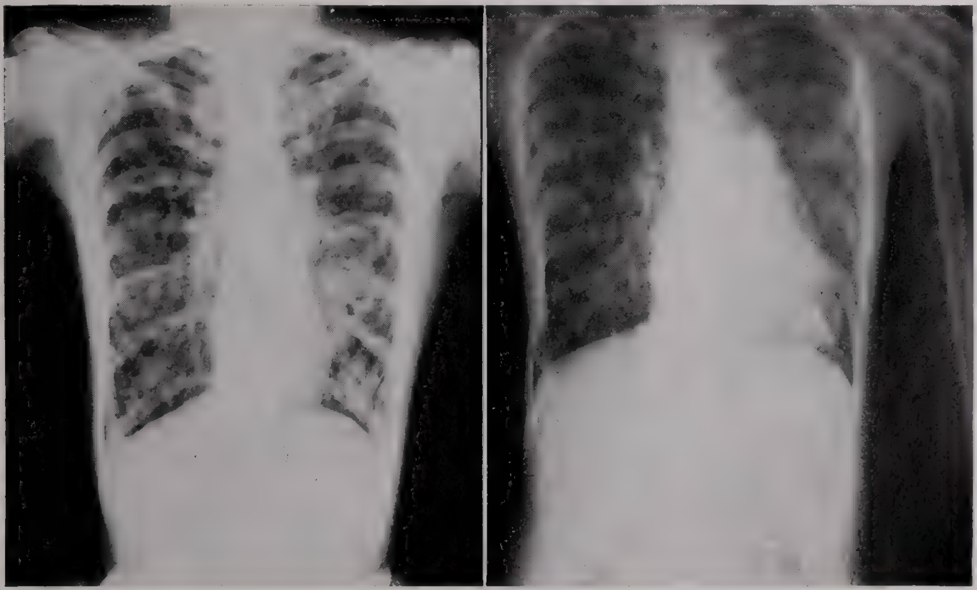

Fig. 12—Acute cardiac dilatation which took place over a six-week interval in an 18-year-old girl with severe advanced pulmonary disease.

Staphylococcus aureus in the sputum in the early stages of the disease, it is remarkable that childhood staphylococcal pneumonia with pneumatoceles and empyema occur so seldom today in patients with cystic fibrosis (Figure 11). Over half of our patients in whom this has occurred are from three to nine months of age when the serum gamma globulin levels are at their physiological lowest. All have required tube thoracotomy drainage and have shown few sequellae related to the empyema itself.

Cor Pulmonale

Finally, the end result of many of the above pulmonary complications, either singly or in tandem, produces enough pulmonary hypertension to cause right heart failure or cor pulmonale.[9] The early stages of this are difficult to detect clinically since an enlarged liver, distended neck veins, right ventricular hypertrophy on electrocardiogram, rales and an increased respiratory rate may all be due to the severe pulmonary disease alone. X-ray evidence of dilatation of the main pulmonary arteries and of progressively increasing heart size (Figure 12) is accurate and practical in the early diagnosis of cor pulmonale. This finding, coupled with peripheral edema, carries a very poor prognosis, with death usually resulting within six months.

Conclusion

Although these severe complications are associated with a high mortality, the general prognosis of cystic fibrosis is steadily improving. The establishment of the diagnosis shortly after birth plus a constant therapeutic and supportive program has extended the life span into the young adult years in over 70% of patients.[10]

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Chronic Enteritis

II Chronicles 14-15: Behold, with a great plague will the Lord smite thy people, and thy children and thy wives, and thy goods: And thou shalt have great sickness by disease of the bowels, until thy bowels fall out by reason of the sickness day by day.

Talmudic description of genital diseases which correspond somewhat to cervical cancer.

Philosopher: a person who says he doesn't care which side his bread is buttered on, because he eats both sides anyway.—Jacob Braude: Speaker's Encyclopedia

Pulmonary Failure in Asthma and Cystic Fibrosis*

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MANY SYSTEMIC and pulmonary diseases terminate in the final common denominator of respiratory failure. The term respiratory failure has different connotations because respiration involves two separate and distinct processes. The first of these, external respiration, is the gaseous exchange that takes place in the lungs and involves the movement of oxygen from the atmosphere into the blood and the movement of gaseous wastes from the blood into the atmosphere. The second process is termed internal respiration and comprises the exchange of oxygen between blood and body cells, cellular utilization of the oxygen, and removal of the waste products of oxidation by the blood. In this discussion we will focus our attention on failure of the first process, external respiration and, to avoid confusion, use the term *pulmonary failure.*[1]

Clinical Manifestations

The function of the pulmonary system is to secure gas exchange between blood and ambient air in order to maintain blood gas tensions within normal limits. From a functional viewpoint pulmonary failure is the impairment of gas exchange to such a degree that arterial blood gas tensions depart from these limits.

Hypoxia

This is a laboratory, rather than a clinical definition, but it is necessary because the clinical manifestations of hypoxia, which include restlessness with impairment of mental function and judgment, hypotension, tachycardia and cyanosis, are not specific enough for precise diagnosis. Unfortunately even central cyanosis—the blue color of the mucous membranes where blood flow is high—is not a reliable sign even under the best conditions.

Hypercapnea

Pulmonary failure may also be manifested as hypercapnea. The clinical symptoms and signs of hypercapnea are also of little help in the diagnosis of pulmonary failure. They include headache, dizziness, confusion progressing to unconsciousness, twitching, hypertension and sweating. Campbell cautions that the only symptom regularly present in hypercapnea is a disturbance of consciousness;[2] Christie states: "The diagnosis of carbon dioxide . . . is a matter of knowledge and of laboratory technique rather than of clinical acumen."[3]

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*Read at the Regional Continuation Course on Chronic Respiratory Diseases in Children and Adolescents at the University of Minnesota, Minneapolis, September 17, 1968.

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Arterial Oxygen and Carbon Dioxide Tension

Because the clinical manifesations of hypoxia and hypercapnea are of little help in the diagnosis of pulmonary failure, clinicians and physiologists must utilize laboratory blood gas measurements. Most authors agree that pulmonary failure is present when there is an acute lowering of arterial oxygen tension to less than 50 mm Hg or an acute elevation of arterial carbon dioxide tension to greater than 50 mm Hg.[2,4,5] Thus the lungs fail in terms of function.

Recent technical developments make the determination of arterial blood gas quickly available and accurate. The technique of arterial puncture can be mastered by anyone who can do a venipuncture. For repeated determinations the placement of an indwelling arterial catheter is recommended. The measurement of arterial oxygen tension (PaO_2) by the Clark membrane-covered polarographic electrode is simple and reliable. The arterial carbon dioxide tension ($PaCO_2$) may be calculated by measuring pH and the CO_2 content of the blood. The Severinghaus electrode permits direct measurement of the arterial carbon dioxide tension. In many medical centers resident and intern physicians have effectively used both the O_2 and CO_2 electrodes.

Evaluation of Therapy

When one has diagnosed pulmonary failure he is well on the road to therapy. The basic principle of treatment in acute pulmonary failure is to deal with potentially reversible features while providing support to correct hypercapnea and hypoxemia. In planning therapy one must evaluate three factors: (1) the nature and severity of the underlying disease; (2) the precipitating factor in pulmonary failure; and (3) the correctable aspects of the crisis.

The remainder of the discussion is concerned with the mechanisms and therapy of pulmonary failure in two diseases: bronchial asthma and cystic fibrosis.

Bronchial Asthma

The American Thoracic Society defines bronchial asthma as "a disease characterized by an increased responsiveness of the trachea and bronchi to various stimuli, and manifested by widespread narrowing of the airways that changes in severity either spontaneously or as a result of therapy."[6] The fundamental functional disturbance in bronchial asthma is airway narrowing or obstruction due to hypertrophy of the smooth muscle, glands and mucosa in response to allergen-antibody stimuli.

The disease occurs in about 3 per cent of the United States' population and the incidence is about the same in children and adults. The old adage, "He who has asthma pants on to a ripe old age," is a misconception; of approximately 4,900 persons who died of asthma in 1962,[5] 216 were less than 20 years old.[7] Pediatric fatalities as the result of this potentially reversible disease are regrettable occurrences.

Mechanism of Failure

The bronchial obstruction of asthma makes the movement of air into and out of the lungs more difficult. During ventilation, air moves from an area of greater to an area of less pressure; on inhalation, air passes through the airways into the alveoli because muscular forces have enlarged the chest and decreased alveolar pressure. The reverse situation occurs during exhalation. The French physician, Jean Marie Poiseuilli, did much to explain why patients with bronchial narrowing have so much trouble breathing. He studied the relationships of various factors to the volume of flow through a tube and derived the equation:

$$\dot{V} = \frac{Pr^4}{8\ lN}$$

where

$\dot{V}$ = volume of flow per second (cm^3/sec)
P = the difference in pressure between the two ends of the tube (dynes/cm_2)
r = the radius of the tube (cm)
l = the length of the tube (cm)

N = the coefficient of viscosity (poises). Examination of this law indicates that the flow through a bronchiole depends on changes in the radius and in the pressure, since viscosity and length do not change appreciably.

A specific example may demonstrate the importance of maintaining an adequate radius of the lumen of the airway. If there is no change in the pressure differential along a bronchus and the radius is decreased by one half, the volume of flow is reduced to 1/16 of the previous value (1/2 to 4th power is 1/16). Obviously decreasing the bore of the airway by such things as bronchospasm, mucosal edema and secretions has a drastic effect on the volume of ventilation. Thus, if the patient can increase the pressure change 16 times he will achieve the same volume of inspiration as if he had no decrease in bronchial radius. The narrowed airway also results in the usual passive exhalation becoming an active process requiring additional energy expenditure. The patient must ventilate even more to supply the increased oxygen needs of the respiratory muscles required by the extra work.

When the expiratory force fails to expel the inspired tidal volume, trapping of air occurs in the lung; as a result the diaphragm is displaced downward and mechanically becomes less efficient in its work. The anteroposterior diameter of the resting lung is increased and the respiratory muscles are less efficient. Under resting conditions only about 1 per cent of the body's energy expenditure is due to the work of breathing. With the exaggerated respiratory efforts of status asthmaticus and the inefficiency of the muscles, 30 to 40 per cent of the body's energy expenditure may be for the work of breathing.[8]

Heart failure may result from the patient's inability to expel the inspired tidal volume; the alveoli become hyperinflated and increase the resistance of the pulmonary capillary bed through which the right heart must propel its blood. Indeed, Miyamoto[9] found that asthmatic children showed a tendency toward right ventricular failure.

The injudicious use of sedation may lead to carbon dioxide retention. Moderate sedation long has been considered an important aspect of treatment since anxiety and agitation may contribute to CO_2 production and ventilatory insufficiency. The use of barbiturates, tranquilizers, and opiates may be beneficial, but the degree to which a small dose of such agents can depress respirations of a patient in pulmonary failure must be recognized. In fact, sedatives and tranquilizers are contraindicated in the management of severe asthma unless ventilation is supported, since their administration has been incriminated as an important contributory factor to death.[10,11]

Precipitating Causes of Failure

Viral or bacterial infection of the respiratory tract is a frequent precipitating cause of acute pulmonary failure, especially in children less than one year of age.[10] Richards found that 31 per cent of pediatric patients with status asthmaticus had pneumonitis when admitted to the hospital,[10] and Lanoff pointed out that pneumonitis was a leading cause of death in asthmatic children.[7]

Clinical Indications of Failure

Downes and Wood[12] listed the following clinical signs as indications of acute pulmonary failure in patients with status asthmaticus:

1. Severe inspiratory retractions
2. Absence of inspiratory breath sounds
3. Generalized muscular weakness
4. Decreased level of consciousness and response to pain
5. Cyanosis in 40 per cent ambient oxygen
6. Arterial carbon dioxide tension of 65 mm Hg or higher.

They stated that at least three of these criteria were necessary to establish a diagnosis of pulmonary failure, but the most useful sign was an increased arterial carbon dioxide tension.

Treatment of Pulmonary Failure in Asthma

The correction of hypoxia and hypercarbia is of prime importance in the treatment of pulmonary failure. If the patient is apneic or gasping, assisted ventilation must begin immediately. Mouth-to-mouth resuscitation should be instituted until appropriate equipment can be secured. If possible, 100 per cent oxygen should be supplied to the patient by intermittent bag breathing through a face mask from an anesthesia machine or from a portable resuscitator connected to oxygen. If exhalation is prolonged and incomplete, gas exchange may be facilitated by gentle manual compression of the thorax during exhalation to help expel air trapped in the lung;[12] such assisted ventilation with high flows of oxygen may sustain life for hours. In patients who are obstructed or poorly cooperative the insertion of an artificial airway is mandatory.

Ventilation

Mechanical ventilation is the most effective management of prolonged pulmonary failure. A *tracheostomy* or *endotracheal tube* is essential for its effective use.[13] In children, nasotracheal intubation is preferred because it is easily and rapidly undertaken even in difficult locations; it produces fewer complications and when improvement occurs in the patient's condition the tube can be easily removed.[10,13] With *nasotracheal intubation* there is no wound to bleed or become infected and less danger of surgical pneumothorax than with tracheotomy; however, the endotracheal tube is prone to cause subglottic edema after extubation. Otherwise the incidence of complications from the two methods of maintaining an airway is about equal.

Once intubation is accomplished the patient is usually connected to a pressure breathing apparatus. This unit provides a number of therapeutic approaches to the problem of hypoxia and hypercarbia:

1. By taking over the total work of breathing and allowing the patient to rest, it decreases the metabolic rate and oxygen consumption.
2. The ventilator may provide a more even distribution of ventilation. This is achieved by decreasing inspiratory flow rate and briefly sustaining pressure near peak-inspiratory volume.
3. Oxygenation is improved both by more efficient ventilation and by the increased oxygen tension of the inspired mixture.
4. Time is gained for medical therapy.

Sedation

In order that patients in pulmonary failure may breath with the respirator some type of sedation is necessary. Downes[12] recommends intravenous pentobarbital, 0.5-1.0 mgm/lb each three to six hours. Adams[14] advocates the use of 0.1 mgm of morphine per kilogram every four hours and does not hesitate to give relaxants to facilitate ventilation. Sedation may also be produced by inhalational anesthesia with diethyl ether or halothane. Bendixen[15] reported that 58 per cent of patients in status asthmaticus were improved by the administration of ether. Halothane anesthesia has given dramatic relief to some patients suffering asthma attacks.

Mucus plugs are an important, correctable cause of pulmonary failure in the asthmatic patient.[16,17] Bohrod[18] noted the omnipresence of plugs when he studied lungs of victims of status asthmaticus from two to 71 years of age. He stated: "The pathologic picture was remarkably constant. The gross appearance of the lungs leads to the inevitable conclusion that dyspnea, anoxia and death were the result of plugging the bronchi by thick tenacious mucus plugs."

The plugs appear for a number of reasons. These patients inhale a large volume of dry gas. The gas is humidified from the airway mucus which results in the mucus becoming tenacious and forming plugs. The formation of plugs is also facilitated by an inadequate fluid intake in patients who are working so hard to breathe. The administration of sympathomimetics also produces viscid secretions. These factors tend to cause secretions to be viscous and tenacious and require therapy aimed at liquefaction and removal.

Hydration

The inhaled gas should be properly humidified so as to render it saturated at body temperature. Adequate hydration is most essential in liquefying secretions. An estimate of the degree of dehydration can be made from the history, based on the amount of fluid intake, vomiting, urinary frequency, fever and weight change. Fluid therapy is most efficiently administered by the intravenous route.

Saline Lavage

Richards[10] and Logan[17] noted that when a nasotracheal tube is in place saline lavage of the respiratory tree has been used with success to remove secretions. This may be accomplished by injecting into the endotracheal tube 10 to 15 cc of saline warmed to body temperature, ventilating the patient two or three times, and then using an appropriately sized catheter to aspirate the returns by a sterile technique. Mist is an effective expectorant which prevents drying and facilitates liquefaction of secretions; appropriately sized mist particles may be delivered by the pressure breathing apparatus. Iodides may be useful as expectorants and are given intravenously as sodium iodide.[10]

Relieve Bronchospasm

Bronchospasm is an important correctable factor in the pulmonary failure of asthma. The narrow bronchi and bronchioles are a result of smooth muscle spasm. As the disease progresses, the narrowing of the airway becomes so severe that wheezing ceases, especially in children. This loss of wheezing is one of the ominous signs of pulmonary failure.

In patients with asthma the use of epinephrine or theophylline will usually improve aeration by relief of bronchiolar spasm. This does not often happen in status asthmaticus since these patients have become "epinephrine fast." Because these children do not respond they often receive large doses of sympathomimetics which cause symptoms of overdosage and make the pulmonary failure more severe.

Aminophylline is one of the most effective bronchodilating drugs and, for the treatment of intractable asthma, is usually given by the intravenous route. It directly relaxes the bronchoconstrictor muscles. Over-zealous treatment with aminophylline causes irritability, restlessness, convulsions and, finally, coma. Therefore aminophylline should be used sparingly—about 100 mgm for infants and 250 mgm for older children.[19]

Corticosteroids

Corticosteroids are useful in the management of status asthmaticus; the reduction in mucosal edema, inflammatory reaction, epithelial desquamation, and mucous gland activity may produce a dramatic improvement in airway obstruction. The dosage varies from 50 to 200 mgm of cortisone or its equivalent a day in four divided doses and depends more upon the severity of the disease than upon the age or weight of the patient.[20]

Correction of Metabolic Acidosis

Acidosis is an additional reversible factor which contributes to mortality in pulmonary failure in status asthmaticus. As arterial tension falls the tissues are forced to utilize anaerobic metabolism. Small elevations in lactic and pyruvic acid appear in the blood.[12] These and other organic acids produce an acidosis in over 75 per cent of pediatric patients in status asthmaticus.[21] The younger the patient the more severe the acidosis. Metabolic acidosis associated with pulmonary insufficiency in asthma has been under-emphasized, especially in the pediatric group. The metabolic acidosis results from inadequate caloric intake, marked exercise of respiratory muscles, excessive use of sympathomimetic amines, dehydration and hypoxia. The combined metabolic and respiratory acidosis progresses rapidly and, unless ventilation is augmented, circulatory depression and cardiac arrest will occur.

Cardiac depression is one of the severe consequences of acidosis. The rationale for the correction of arterial pH is based upon the improvement in systemic and coronary circulation which follows intravenous administration of sodium bicarbonate to acidotic experimental animals.[22] The resultant decreased resistance in the cardiac and systemic vascular beds improves tissue perfusion. Another consequence of acidosis is pulmonary vasoconstriction.[10] Liljestrand recently concluded that an increased hydrogen ion concentration in the blood is a chemical stimulus for pulmonary vasoconstriction.[23]

Acidosis also results in a less efficient transport of oxygen as a consequence of the "Bohr effect." When hemoglobin is acidotic the oxygen dissociation curve shifts to the right and a higher oxygen tension is required to achieve a given oxygen saturation in the blood. In a patient already hypoxemic the shift only intensifies tissue hypoxia.

At an acidotic pH, cellular oxidative enzymes function poorly because the mass action of CO_2 inhibits the decarboxylation process. Because of this the cells utilize anaerobic metabolic pathways and increase the lactate pyruvate ratio in the blood.[10] This intensifies the metabolic acidosis.

Perhaps the most important consequence of acidosis in pulmonary failure for the patient with asthma has to do with the action of sympathomimetic drugs. Bridget and Visscher[24] pointed out in 1927 that adrenaline works best in an alkaline medium. Blumenthal[25] stated that nothing was more disturbing in treating the asthmatic patient than to find that epinephrine, the best drug in treating an acute attack, was losing its effectiveness. He indicated that the decreasing arterial pH diminished the response to epinephrine and resulted in the so-called epinephrine-fast asthmatic.

The prevention of the consequences we have just described demands that acidosis be corrected. But when is it severe enough to need correction? Most workers[13,14,26] agree that if the pH is less than 7.20, then the factors discussed above are operating significantly.

Sodium bicarbonate and THAM* [Tris(hydroxymethyl)aminomethane] act directly and rapidly in correcting acidosis. Sodium bicarbonate binds the H^+ with its HCO_3 radical and displaces the reaction $CO_2 + H_2O \longleftrightarrow H_2CO_3 \longleftrightarrow H^+ \; CO\text{-}_3$ to the left by generating more H_2CO_3 and more CO_2.[12] The THAM buffer might appear preferable in status asthmaticus since its buffering action is not dependent upon the excretion of carbon dioxide. THAM binds H^+ with its amine radicle and decreases carbon dioxide concentration by displacing the reaction to the right. If renal function is adequate the resultant bound H^+ is rapidly excreted. THAM is not without hazard, however, as it may produce respiratory depression and should not be administered unless ventilation may be assisted. Because THAM produces a stronger alkalizing effect than other agents, frequent determinations of acid base variables must be obtained.

It is often difficult to determine the amount of alkalizing required. If the apparatus used to determine blood gases is an Astrup unit, the Siggaard-Anderson nomogram will give the base excess (B. E.).[27] A negative base excess means that a basic deficit exists and more base is required. The formula that can be used is millimoles of THAM = – base excess (mEq./L) x body weight (K) x 0.3. The factor 0.3 takes into account the volume of extracellular fluid (assumed to be 20 per cent of body weight) and the unionized fraction of tris (30 per cent at pH 7.40).[28] In most instances a 0.3M solution of THAM, an isosmotic solution with body fluids, should be used. Then the formula is simplified to:

$$\begin{aligned}\text{ml of 0.3M THAM} &= -\text{base excess x body wt (Kg) x } 0.3 \times 3.33\\ &= -\text{base excess x body wt (Kg)}\\ &\qquad (\text{mEq/L})\end{aligned}$$

THAM comes in an ampule of 36 grams. When mixed with 1000 cc of diluent, a 0.3M solution results. While the solution is being prepared, sodium bicarbonate may be given to correct the acidosis. This may be administered as rapidly as 9 mEq per minute.[10] A useful formula for bicarbonate dosage is:

$$NaHCO_3 \text{ (mEq)} = \frac{\text{body weight (kg)}}{5} (-BE).$$

Correction of Respiratory Acidosis

Mechanical ventilators are the most effective method of managing respiratory acidosis in children with status asthmaticus.[8,13,21] The choice of respirator is dictated by availability, the familiarity of the therapeutic team with the machine and the special requirement of the patient. The measurement of expired minute ventilation by a respirometer at the time of arterial sampling is necessary to monitor therapy. The aim should be to remove CO_2 over a period of several hours, but no faster than 10 mm Hg carbon dioxide tension per hour. Unless carbon dioxide is removed slowly seizures and shock may occur.[29] If therapy with the ventilator is to be effective secretions must be removed.

The most common cause of pulmonary failure in the pediatric asthmatic patients is a respiratory tract infection. When instituting therapy in these patients a culture and antibiotic sensitivity should be obtained so that the appropriate antibiotic may be begun if pathogens are present. If infection occurs during therapy prompt investigation and treatment is mandatory.

Cystic Fibrosis

In contrast to the pulmonary failure seen in status asthmaticus that of cystic fibrosis is almost completely a consequence of the unique viscid tracheobronchial secretions which account for most of the morbidity and 90 per cent of the mortality.[30] The primary pulmonary lesion of cystic fibrosis is partial bronchial obstruction by secretions.[31] The ciliary activity, expired air flow, and coughing which move normal mucus freely are ineffective in preventing the accumulation of the thick, viscid mucus of the disease.

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*Tham is also called Tris, Tris buffer, Tris amino. Talatrol (Abbott) is the trade name of the medically available preparation.

Inhaled bacteria are deposited on the stagnant mucus and propagate to produce local infection. Infection increases obstruction and further impairs the clearance of secretions by producing mucosal edema, inflammation, and exudation of inflammatory debris into the mucus. In response to inflammation more secretions are produced, until the final result is a vicious cycle of accumulating secretions, airway obstruction, infection, infection causing more obstruction and increased secretion. The important point in therapy is that, although the early stage of the lesion is reversible, if infection persists, the ciliated pulmonary epithelium is destroyed and the resulting squamous metaplasia produces permanent impairment of the cleaning mechanism of the airway.[30] If extensive damage occurs, bronchiectasis, abscess formation and peribronchial fibrosis result. The lesions progress to obstructive emphysema and cystic bronchiectasis. The functional residual capacity increases while vital capacity diminishes; the end result is severely limited respiratory movements, poor aeration with increasing hypoxia and carbon dioxide retention.

The diagnosis of acute pulmonary failure in cystic fibrosis requires a high level of clinical suspicion and patient observation. If the clinical signs and symptoms of pulmonary insufficiency are present, laboratory confirmation is indicated.

The Management

The management of acute pulmonary decompensation must be aimed at ventilation and removal of secretions since the basic defect in the disease is unknown. The initial step in therapy requires establishing an airway to provide a pathway for the removal of the bronchial secretions which usually have caused the pulmonary failure. We prefer nasotracheal intubation to tracheotomy because the artificial airway is seldom maintained for more than 24 hours. When intubation has been accomplished one first removes the gross secretions causing the failure and sends a sample of these to the laboratory for bacterial culture and antibiotic sensitivity tests. Often the thorough cleansing of the airway is sufficient to produce a dramatic improvement in the patient's condition.

The Airway

Since the establishment of an artificial airway removes the patient's method of humidifying inhaled air, one must supply properly humidified gases to prevent further drying of the viscid secretions. Aerosol therapy of appropriately sized particles will aid liquefaction. Edema in the airway may be reduced by administering nebulized neosynephrine which, because of its rapid action on the mucosa and its few side reactions, is the vasoconstrictor of choice. In addition to systemic antibiotics the areas of local infection in the lungs may be treated by nebulizing a suitable antibiotic through the airway directly to the site of infection.

Liquefying Mucus

Webb reported on his experience with acetylcysteine, a relatively new agent that is effective in liquefying mucus. The action of this agent is due to its dissolution of the disulfide bonds found in mucus. The agent may be given via a nebulizer.

Bronchial Lavage

Cenzlaux[32] recently compared the relative benefits and hazards of bronchial lavage involving 10 per cent acetylcysteine with that utilizing sodium chloride solution in a similar group of patients. He found that patients whose airways were lavaged with acetylcysteine had an increased arterial carbon dioxide tension and a decreased arterial oxygen tension immediately after treatment; those treated with NaCl had no change in blood gases. He also found that, regardless of the agent, pulmonary functions were reduced for two or three days but, if the lavage was part of a complete therapeutic program, improved pulmonary function could be demonstrated two to six weeks after therapy.

Positive Pressure Breathing

Positive pressure breathing apparatus is useful in providing short term ventilation and in the administration of local antibiotics and other medications. Its prolonged use results in an increase in functional residual capacity and a reduction in vital capacity. It should therefore be used only for intermittent treatments lest it do irreparable damage to the patient.

Summary

The basic principle of therapy in managing the pulmonary failure of bronchial asthma and cystic fibrosis is to treat the potentially reversible features while providing support to correct the hypercapnea and hypoxemia. This requires a knowledge of the underlying disease, factors causing the pulmonary failure, and the correctable aspects of the crises.

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It is magnificent to grow old, if one keeps young.—Harry Emerson Fosdick

Cardiac Complications of Chronic Pulmonary Disease in Childhood*

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COR PULMONALE is the major cardiac complication of chronic pulmonary disease. As defined by a committee of the World Health Organization,[1] cor pulmonale is "right ventricular hypertrophy, secondary to disease of the lung parenchyma or pulmonary vasculature, or due to abnormalities of pulmonary function." Specifically excluded as causes are congenital heart disease and pulmonary hypertension secondary to disease of the left heart.

Physiology of Cor Pulmonale

Pulmonary hypertension is the basic underlying hemodynamic constituent of cor pulmonale. Knowledge of the mechanisms responsible for pulmonary hypertension in patients with chronic lung disease is central to our understanding of cor pulmonale. Pressure in the pulmonary artery is dependent on the resistance to blood flow imposed by the pulmonary vasculature. The pulmonary arteriole constitutes the major resistance vessel of the lung. Constriction of the pulmonary arteriole increases pulmonary vascular resistance and results in pulmonary hypertension.

Hypoxia and Hypercarbia

There are three factors common to patients with chronic lung disease which influence vasomotion of the pulmonary arteriole and thus pulmonary artery pressure.

Hypoxia (decreased arterial pO_2) alone has little effect on pulmonary pressure in normal man. Supportive evidence includes the many children with cyanotic congenital heart disease who have normal pulmonary artery pressure. Likewise, isolated hypercarbia (increased arterial pCO_2) has little effect on pulmonary artery pressure.

Acidosis

On the other hand, acidosis, either metabolic

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*Read at the Regional Continuation Course on Chronic Respiratory Diseases in Children and Adolescents at the University of Minnesota, Minneapolis, September 17, 1968.

†Paul F. & Faith S. Dwan, Professor of Pediatric Cardiology, University of Minnesota.

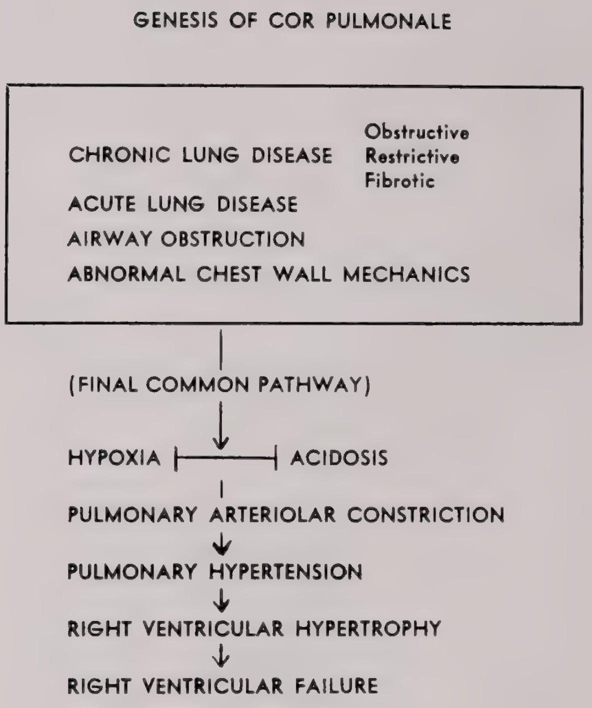
GENESIS OF COR PULMONALE
CHRONIC LUNG DISEASE
Obstructive
Restrictive
Fibrotic
ACUTE LUNG DISEASE
AIRWAY OBSTRUCTION
ABNORMAL CHEST WALL MECHANICS
(FINAL COMMON PATHWAY)
HYPOXIA
ACIDOSIS
PULMONARY ARTERIOLAR CONSTRICTION
PULMONARY HYPERTENSION
RIGHT VENTRICULAR HYPERTROPHY
RIGHT VENTRICULAR FAILURE

Figure 1

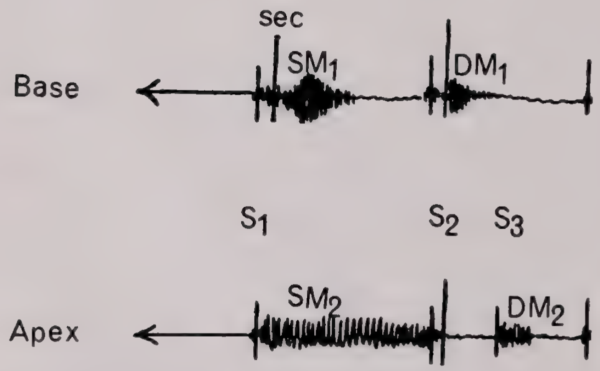
sec
SM1
DM1
Base
S1
S2
S3
SM2
DM2
Apex

Fig. 2—Schematic representation of auscultatory findings in cor pulmonale. At the cardiac base a systolic ejection click (SEC) immediately follows the first heart sound (S1). A systolic ejection murmur (SM1) is the result of turbulence as blood flows into the dilated pulmonary artery. The second or pulmonary component of the second heart sound (S2) is accentuated as a consequence of pulmonary hypertension. When pulmonary insufficiency is present an early blowing, decrescendo diastolic murmur (DM-1) is heard. When right ventricular dilatation is sufficient to produce tricuspid insufficiency, a holosystolic murmur (SM-2) and a mid-diastolic rumble (DM-2) are discerned at the apex. S3 = third heart sound.

or respiratory, significantly increases pulmonary artery pressure and appears to be the major regulator of pulmonary arteriolar vasomotion.[2] Furthermore, acidosis renders the pulmonary arteriole extremely sensitive to the vasocontrictor effects of hypoxia.

Figure 1 summarizes the "final common pathway" from chronic lung disease to right ventricular failure.

Diagnosis of Cor Pulmonale

A careful physical examination almost invariably allows the physician to make a diagnosis of cor pulmonale. The auscultatory features are depicted in Figure 2.

Pulmonary Hypertension

Pulmonary hypertension results in vigorous closure of the pulmonary valve. Since this valve is located in the anterior mediastinum in close proximity to the stethoscope, vigorous valve closure is easily detected as a *loud snapping second sound*. Accentuated pulmonic closure is best heard in the second, third, and fourth left intercostal spaces. Usually the second sound is not split widely and the splitting varies normally with respiration. Pulmonary hypertension also leads to dilatation of the main pulmonary artery. As a consequence of the disparity between the size of the pulmonary artery and the annulus of the pulmonary valve, turbulence is created as blood flows through the pulmonary outflow area, producing *a systolic ejection murmur*. The *systolic ejection click*, a sharp sound immediately following the first sound and heard along the lower left sternal border, is also commonly heard in patients with pulmonary hypertension. Pulmonary insufficiency is occasionally present in pulmonary hypertension and produces a *decrescendo early diastolic murmur* in the pulmonic area.

Right Ventricular Hypertrophy

The features of right ventricular hypertrophy include an accentuated right ventricular heave or lift which is maximal at the sternum. As the right ventricle dilates it creates enlargement of the tricuspid valve ring. The resultant tricuspid insufficiency produces a *holosystolic murmur* at the lower left sternal border and increases the amount of blood which must return from right atrium to right ventricle during diastole. The augmented diastolic flow produces the tricuspid flow murmur, a *mid-diastolic blowing murmur* heard best at the left sternal border in the fourth, third and second intercostal spaces.

Right Ventricular Failure

In addition to these signs of pulmonary hypertension and right ventricular hypertrophy, features of right ventricular failure are helpful when present. These include hepatomegaly, distended neck veins, peripheral edema and a prominent 3rd heart sound (systolic gallop rhythm).

Thoracic Roentgenogram

The most characteristic feature of the roentgenogram is enlargement of the pulmonary artery segment (Figure 3); the major pulmonary arteries are also enlarged. There is disparity between the accentuated proximal vascular markings and the normal distal vascular markings. Dilatation of the right ventricle and enlargement of the right atrium are observed in some patients.

Electrocardiogram

The electrocardiogram is variable in cor pulmonale because it is influenced not only by cardiac chamber enlargement, but by unusual positions of the heart in the chest, by changes in pulmonary volume, and by abnormalities of the thorax. Patients with chronic lung disease may have one or more of these factors.

The most helpful feature is electrocardiographic evidence of right atrial enlargement, which consists of tall peaked P waves (Figure 4). The tall P wave may be present in only one or in several of the following leads; I, II, III, AVL, AVF, VI and V2.

Electrocardiographic evidences of right ventricular hypertrophy are more variable since these may be masked by pulmonary and thoracic abnormalities. Right ventricular hypertrophy can be identified by the following features: upright T in leads V4R and V1 (between the ages of one week and eight years); and tall R in V_1 (greater than 20 millivolts) and/or a deep S in V6.

These physical and laboratory findings define the presence of pulmonary hypertension and the magnitude of right ventricular hypertrophy. Evidence of right ventricular failure indicates a severe degree of cor pulmonale and demands immediate and vigorous therapy.

Treatment

A review of the "final common pathway" (Figure 1) identifies the various areas to which treatment might be directed. Thus, we may attempt to improve the underlying pulmonary or thoracic disease, to correct hypoxia and/or acidosis, to alleviate pulmonary arteriolar constriction or to treat right ventricular failure.

Treatment of the underlying pulmonary or thoracic disease must be the primary goal and is the most effective. Treatment directed to the pulmonary problem must be vigorous, aggressive and continuing.

Oxygen

The goal of treatment is improvement of oxygenation while avoiding development or progression of respiratory acidosis (hypercarbia). Efforts at improving oxygenation may be successful for short periods, but ultimate

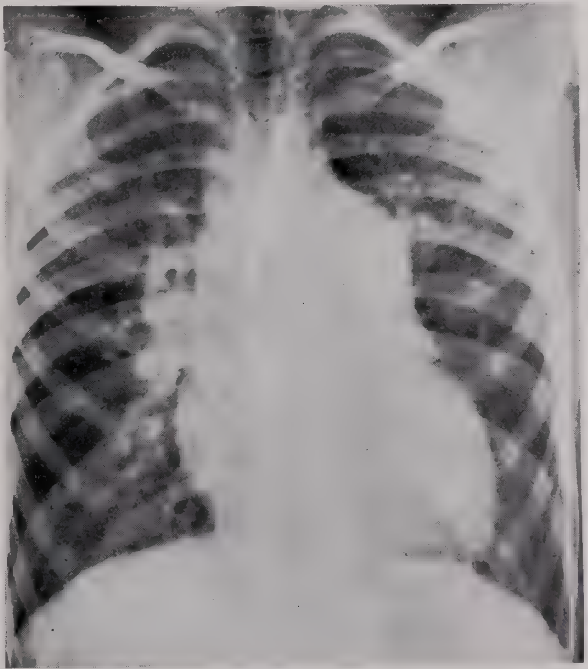

Fig. 3—Thoracic roentgenogram in a 10-year-old child with chronic cor pulmonale. Note the characteristic enlargement of the pulmonary artery segment. There is a disparity between the normal peripheral pulmonary markings and the prominent proximal hilar pulmonary vessels. The heart is not significantly enlarged. There is evidence of diffuse parenchymal lung disease.

success depends upon improvement in the underlying pulmonary disease.

Oxygen therapy in children with chronic lung disease must be approached with caution. Inhalation of oxygen in concentrations greater than 60% over a period of days is toxic in man and animals. However, a more important consideration in a patient with chronic lung disease is the frequent association of hypercarbia. When hypercarbia has been present the respiratory center may no longer respond to changes in pCO_2. In this situation hypoxia provides the drive for respiration. Inhaled oxygen, by alleviating hypoxia, thus removes the respiratory drive, allows a decrease in ventilation, and results in a rise in pCO_2 and in CO_2 narcosis. Prevention of CO_2 narcosis requires that oxygen therapy be combined with artificial ventilation; but oxygen therapy with or without positive pressure ventilation provides only a temporary respite: time which must be used to relieve the underlying lung disease.

Buffer Solutions

Acidosis alone produces pulmonary hypertension and in addition makes the pulmonary arteriole more sensitive to the vasoconstrictor effects of hypoxia. Acidosis may also be controlled for short periods of time with buffer solutions such as sodium bicarbonate or tris buffer. Administration of these agents must be carefully monitored with blood gas determinations.

Pulmonary Arteriolar Vasodilatation

While it is possible to dilate the pulmonary

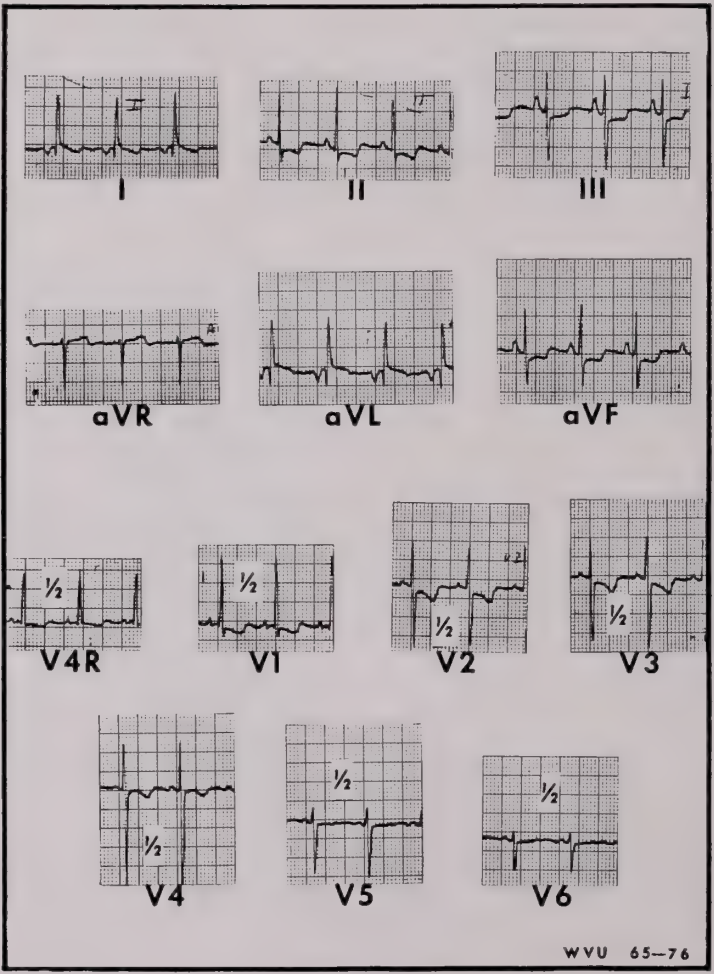

Fig. 4—The electrocardiogram in a five-year-old child with cor pulmonale. Right atrial enlargement is reflected by prominent peaked P waves in lead III only. The tall R waves in V4R and V1 and the deep S waves in V5 and V6 reflect pressure hypertrophy of the right ventricle. ½ = half standard.

arterioles with infusion of acetylcholine into the pulmonary artery or by the administration of isoproterenol or Priscaline,® the effects of these agents are short-lived and capricious and require continuous hemodynamic monitoring. They have not achieved clinical usefulness.

Improvement of Cardiac Function

Digitalization

Right ventricular failure dictates immediate efforts to improve cardiac function. Simultaneous efforts must be made to improve ventilation and oxygenation.

In our experience digoxin (Lanoxin®) is the most useful digitalis glycoside. Our dosage schedule is:

Total digitalizing dose (TDD) of digoxin (Lanoxin®)

Prematures and neonates (first 30 days)	0.035mg/k
One month to two years	0.05 mg/k
Over two years	0.035mg/k

One half of total digitalizing dose initially 1/4 in six hours, 1/4 in 12 hours, (I.M.). Maintenance to start 24 hours after first dose; 1/7 of total digitalizing dose bid. Owing to the variability of response to digoxin, patients must be monitored carefully and the dosage altered accordingly.

Diuresis

Diuretic therapy provides good short-term symptomatic relief until definitive therapy of the pulmonary problem is achieved.

Meralluride given intramuscularly is an effective, rapid-acting diuretic. Our dosage schedule is premature and neonate 0.1 ml; infant, 0.25 ml; 1-5 years, 0.5 ml; 5-12 years, 1.0 ml. This dose may be repeated daily for three days.

Intravenous ethacrynic acid is a potent diuretic for use in critical situations; but the electrolyte status must be determined before this drug is used, and the fluid and electrolyte balance carefully monitored after dosage, since salt and water loss may be massive.

The usual dosage of ethacrynic acid is 1 mg/k intravenously over a 10-minute period. This dose may be repeated in six hours, but only after measurement of the patient's fluid and electrolyte status.

Summary

Whatever the nature of the underlying pulmonary problem, the genesis of cor pulmonale can be represented by a "final common pathway" from acidosis and hypoxia to right ventricular failure.

An understanding of this pathway permits the diagnosis of cor pulmonale and provides the basis for rational therapy.

The sine qua non of treatment of cor pulmonale is improvement of pulmonary function. The purpose of therapy directed to the cardiac problems is to buy time which must be utilized in the vigorous treatment of the underlying pulmonary problem.

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Science

Science is the great instrument of social change, all the greater because its object is not change but knowledge, and its silent appropriation of this dominant function, amid the din of political and religious strife, is the most vital of all revolutions which have marked the development of modern civilization.

—A. J. Balfour, Scientific Monthly

If all the neglected Bibles were dusted simultaneously, we would have a record dust storm and the sun would go into eclipse for a whole week.—David Nygren

WHAT'S
SO WEAK
ABOUT
THE WEAKER
SEX?

OFTEN...
HER LOWER
G. I. TRACT

Psycho-abdominal Distress: Frequently Female

Women aged 15 to 45 appear to be more prone than men to bloating, cramping pain of stress-related intestinal disturbances such as irritable or spastic colon.[1,2]

Frequently Recurrent

In the experience of many physicians, women are more likely to reappear time after time with repeated complaints of lower G.I. distress.

Requiring Definitive Therapy

Often needed is therapy adequate to control both the somatic and the emotional components of psycho-abdominal complaints.

Definitive Dual Therapy

'Milpath' contains a proven synthetic anticholinergic useful for relieving hypermotility, spasm, and hypersecretion of the gastrointestinal tract.

In addition, 'Milpath' provides a time-tested tranquilizer for mild but effective anti-anxiety action.

With Flexible Dosage

- 'Milpath'-400 (meprobamate 400 mg. + tridihexethyl chloride 25 mg.) Usual adult dose: 1 tablet *t.i.d.* and 2 at bedtime.
- **When less tranquilization is required: 'Milpath'-200 (meprobamate 200 mg. + tridihexethyl chloride 25 mg.)**

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gently but firmly

MILPATH®

(meprobamate + tridihexethyl chloride)

relaxes smooth muscle and psyche

Please see the following page for brief summary of prescribing information.

Gently but firmly MILPATH®

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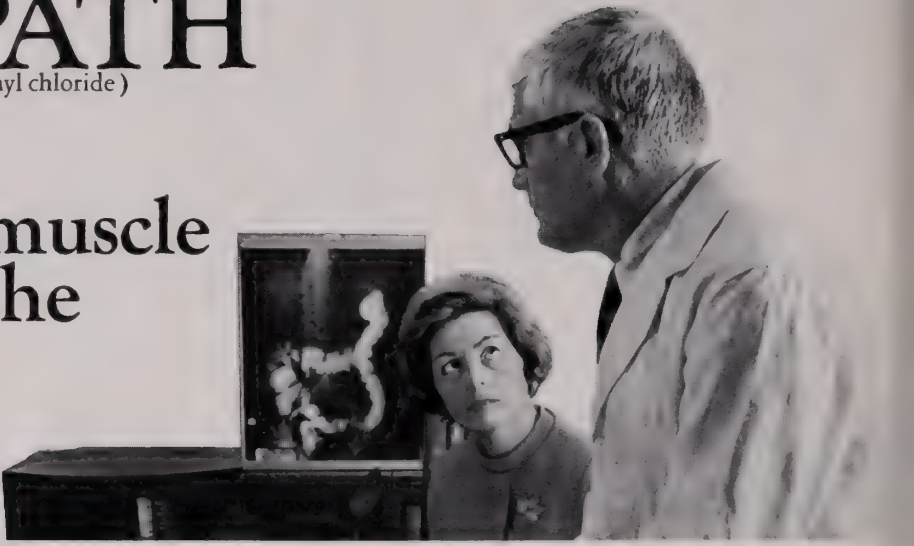
Relaxes smooth muscle and psyche



Usual Adult Dosage

One 'Milpath'-400 tablet, three times a day at mealtimes, and two at bedtime. For greater anticholinergic effect, two 'Milpath'-200 tablets, three times a day at mealtimes and two at bedtime. Doses of meprobamate above 2400 mg. daily not recommended.

Indications

Useful in organic and functional disorders with hypersecretion and hypermotility of G.I. tract, especially when accompanied by anxiety, neurosis, or tension states. Should be used as an adjunct to all other therapeutic measures.

Contraindications

Tridihexethyl chloride: Urinary bladder-neck obstructions, e.g., prostatic obstruction due to hypertrophy; pyloric obstructions because of reduced motility and tonus: organic cardiospasm (megaesophagus); glaucoma; possibly in stenosing gastric or duodenal ulcers with significant gastric retention.

Meprobamate: Previous allergic or idiosyncratic reactions to meprobamate.

Precautions

Tridihexethyl chloride: Use cautiously in elderly males (possible prostatic hypertrophy).

Meprobamate: Carefully supervise dose and amounts prescribed. Consider possible dependence or habituation (reported occasionally after excessive use), particularly in severe psychoneurotics, alcoholics, ex-addicts. Withdraw gradually (one or two weeks) after excessive dosage for weeks or months to avoid recurrence of pre-existing symptoms (e.g., anxiety, anorexia, insomnia) or withdrawal reactions (e.g., vomiting, ataxia, tremors, muscle twitching; rarely, epileptiform seizures, more likely in those with CNS damage or latent convulsive disorders). If drowsiness or visual disturbance occurs, reduce dose and advise against activity requiring alertness (driving, machinery operation). Effects of excess alcohol may be increased. Grand mal seizures possible in persons with both petit and grand mal. Prescribe cautiously in small amounts to patients with suicidal tendencies. Prescribe with caution to patients with known sensitivity to compounds of similar chemical structure, e.g., carisoprodol.

Side Effects

The following side effects of components may occur with 'Milpath'.

Tridihexethyl chloride: Severe effects rare on recommended dosage. Anticholinergic effects: dry mouth (fairly frequent at oral doses of 100 mg.), constipation or "bloated" feeling. Possible: tachycardia, dilation of pupils, increased ocular tension, weakness, nausea, vomiting, headache, drowsiness, urinary hesitancy or retention, dizziness.

Meprobamate: Drowsiness, sometimes with ataxia, usually controlled by decreasing dosage, occasionally with aid of central stimulants (e.g., amphetamine). Rarely, allergic or idiosyncratic reactions (usually after one to four doses); in mild form: itchy, urticarial or erythematous, maculopapular rash, generalized or confined to groin. Acute nonthrombocytopenic purpura with cutaneous petechiae, ecchymoses, peripheral edema and fever, transient leukopenia, and one fatal bullous dermatitis (after meprobamate and prednisolone) reported. More severe, very rare hypersensitivity fever, chills, fainting spells, angioneurotic edema, bronchial spasms hypotensive crises (one fatal), anuria, anaphylaxis, stomatitis and proctitis. Treat symptomatically (e.g., epinephrine, antihistamines possibly hydrocortisone); stop and do not restart the drug. Isolated agranulocytosis, thrombocytopenic purpura, one fatal aplastic anemia reported, but only in presence of known toxic drugs, porphyric symptoms reported but relationship not established. Fas EEG activity, usually after excessive dosage. Impairment of visua accommodation reported by one observer. Fixed drug eruption with meprobamate and cross reaction to carisoprodol reported.

Suicidal attempts may produce drowsiness, lethargy, stupo ataxia, coma, shock, vasomotor and respiratory collapse, an death. Excessive dosage has led rapidly to sleep, then reduction o vital signs to basal levels. Empty stomach, and if respiration b comes very shallow and slow, cautiously give CNS stimulants (e. caffeine, pentylenetetrazol, amphetamine); also pressor amines i indicated.

Supplied

In two strengths:
'Milpath'-400: Yellow, scored tablets.
'Milpath'-200: Yellow, coated tablets.
Before prescribing, consult package circular.

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(1928A0

Bacteria in the Sputum*

Pediatric Patients with Chronic Pulmonary Disease

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THE LOWER RESPIRATORY tract is normally sterile. This fact so easily stated is evidence of the remarkably capable host defense mechanism in the lungs. Bacteria are constantly present and are sometimes in high concentration in the air we breath. In spite of this, the magnificent defense mechanism of the lower respiratory tract keeps the lungs sterile. The upper respiratory tract, on the other hand, is never sterile and is simultaneously colonized by several bacterial species. There are poorly understood checks and balances among the different bacterial varieties and the host; but in health the so-called "normal flora," together with potential pathogens, live harmoniously together. As might be expected, there are symptoms of infection when particularly virulent outside bacterial invaders (such as group A streptococci) become the predominant organisms of the upper respiratory tract; but even during these illnesses the sterility of the lower respiratory tract is maintained.

These observations have led to postulation that bacterial invasion of the lower respiratory tract can take place only when there is a preceding non-bacterial injury which reduces the effectiveness of the host defense mechanisms. Traumatic injury to the anatomical barriers, virus injury of the cells of bronchi or alveoli, and obstruction to ciliary action are examples. Therefore, it is not surprising that the bacterial etiology of lower respiratory tract disease is usually a species such as pneumococcus which is typically present in the upper respiratory tract. Pneumococci are frequently recovered from the bronchial secretions of patients with chronic respiratory tract disease and may play a role in the continuing inflammatory response in these patients. This may seem paradoxical since pneumococci are frequently associated with acute pneumonia which is fatal or cured within a few days; however, there are more than 72 capsular types of pneumococci and only a few virulent or acute pneumonia-producing types. The pneumococcal types recovered from patients with chronic pulmonary disease are usually different from those in patients with acute pneumococcal pneumonia.

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*Read at the Regional Continuation Course on Chronic Respiratory Diseases in Children and Adolescents at the University of Minnesota, Minneapolis, September 17, 1968.

Hemophilus Organisms

A similar situation exists with *Hemophilus influenzae*. Hemophilus organisms are also part of the normal flora of the upper respiratory tract, but these are usually non-encapsulated and therefore non-typable. The virulent hemophilus organisms recovered from patients with meningitis or osteomyelitis usually have capsules and are Type B. It must be emphasized here that the presence of pneumococci or hemophilus in lower respiratory tract secretions cannot be considered normal regardless of the type, and they undoubtedly contribute to inflammatory response in this location and should be treated.

There is no correlation between the potential pathogens recovered from cultures of the pharynx and carefully collected secretions from the lungs. Transcutaneous tracheal aspiration or bronchoscopy, therefore, is necessary for collection of pulmonary secretions for culturing.

Staphylococcus Aureus

Staphylococcus aureus is present in the upper respiratory tract of approximately 30% of nearly any population; however, it is an exceedingly infrequent organism in the lower respiratory tract of patients with chronic lung disease, except in those with cystic fibrosis. These patients almost uniformly harbor staphylococci in their bronchi, and the resulting inflammatory response leads to purulent bronchial secretions and eventual parenchymal fibrosis. The association of staphylococcal bronchitis and cystic fibrosis is not a result of immunologic inability, since cystic fibrosis patients uniformly demonstrate high titers of anti-staphylococcal antibodies and their leukocytes show normal ability to phagocytize and kill staphylococci. The basis for this association of pulmonary staphylococci and cystic fibrosis is not known at present, but continuing investigation may help in understanding this crucial relationship.

Concluding Comments

The finding of viable bacteria in a part of the body which is normally sterile serves as a strong stimulus for vigorous antibody therapy with bactericidal antibodies. This response is correct; patients with chronic pulmonary disease are improved by antibiotic therapy, but this alone is *not enough*. The persistence of bacterial products as well as live bacteria in the lower respiratory tract continually stimulates inflammatory responses with infiltration of phagocytic cells, granuloma formation and parenchymal fibrosis. It is necessary therefore that these products be removed. The scrupulous attention to bronchial toilet which characterizes present-day management of cystic fibrosis patients is equally as important as antibiotics in the treatment of the bacteria in the lungs of patients with chronic pulmonary disease.

Pathiatry

This particular cult is trade-marked. "It combines the best principles of spinal adjustment, traction, manipulation, deep massage, etc., administered by oneself. So simple and delightful as to become a part of the daily toilet. Done anywhere, at any time, while standing, even sitting; without appliance of any kind.*

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*Morris Fishbein, M.D.: The New Medical Follies, 1927.

Great eaters and great sleepers are incapable of anything else that is great.—Henry IV of France

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Death is the ugly fact which Nature has to hide, and she hides it well.—Alexander Smith

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Many a family tree needs trimming.
—Frank McKinney Hubbard

Cystic Fibrosis*

Surgical Treatment of Pulmonary Complications

DOUGLAS S. HOLSCLAW, M.D.†
HARRY SHWACHMAN, M.D.†
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As a result of the medical management of infants and young children with the early pulmonary involvement of cystic fibrosis and because of the striking improvement in the surgical management of infants with meconium ileus, there are now a relatively large number of patients with cystic fibrosis who live well into their teens and beyond. Over 90% of all patients with cystic fibrosis show either clinical or x-ray evidence of pulmonary involvement, usually both.

Certain pulmonary complications, if left untreated, will lead to more rapid progression of the disease. Among these are lobar and lobular atelectasis, usually with underlying abscess formation and bronchiectasis; large lung abscess cavities; localized areas of bronchiectasis; lobar botryomycosis;‡ pneumothorax, and empyema. Because of this, we have encouraged palliative pulmonary resection in carefully selected patients.[1] By this, we hope to relieve some of the acute symptoms present and to slow progression of total pulmonary involvement as well. Pulmonary resection in this disease should be undertaken with the full understanding that pulmonary involvement is never limited only to a single segment of a lobe. When proposing resection to the parents of these patients it must be emphasized that this is only a palliative procedure.

Preoperative Evaluation and Management

All patients have been on a full medical program of antibiotics, physical therapy, mist tent, expectorants and usually antibiotic and mucolytic aerosol inhalations. In general, attempts to expand an atelectatic lobe or segment by bronchoscopy and suction have not been successful. We rarely employ bronchograms now

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†From the Division of Clinical Laboratories and the Department of Medicine, Children's Hospital Medical Center and Department of Pediatrics, Harvard Medical School, Boston.

‡See Test Your Word Score Page 1401.

since many of our patients in the past have not tolerated bronchography well. We can now obtain much more information by the comparison of perfusion and ventilatory scans using either the Technetium^{99} labeled albumin microaggregate or Xenon^{133} techniques. In patients who are old enough to cooperate, pulmonary function tests have given a good prediction of the patient's postoperative pulmonary status. In almost all cases, the affected area of lung removed was not of functional value. In cases where an entire pneumonectomy is contemplated, we have utilized cardiac catheterization employing a balloon to occlude the pulmonary artery on the affected side to determine if the remaining lung can withstand the increase in pulmonary blood flow. Differential bronchospirometry may be an additional useful tool when pneumonectomy is being contemplated.

TABLE 2

Pulmonary Resection in 38 Patients with Cystic Fibrosis

Right Side		Left Side	
Upper lobe	6	Upper lobe	2
Middle lobe	8	Upper lobe—biopsy only	1
Upper & middle lobes	5	Lingula	1
Anterior segment upper	1	Lower lobe	4
Middle and lower lobes	3	Lower lobe & lingula	1
Lower lobe	2	Pneumonectomy	3
Pneumonectomy	2		
Total	27	Total	12

TABLE 3

Results of Pulmonary Resections

Excellent	3 (8%)	Symptom-free with full activity
Good	21 (54%)	Definite decrease in symptoms with increased sense of well-being
Fair	6 (16%)	Mild decrease in symptoms with increased sense of well-being
Unsatisfactory	2 (6%)	Unchanged
Poor	6 (16%)	Patient either died as result of operation or is worse.

The patient is brought into the hospital about one week prior to surgery to ensure psychological adjustment to his surroundings and to facilitate vigorous pulmonary toilet. We strongly urge that a tracheostomy be performed some four to six days prior to the thoracotomy. In this manner, the child can adjust somewhat to a new way of breathing, talking and coughing, and the vigorous suctioning that will be necessary in the postoperative period.

Surgical Considerations

Intubation and Operation

Our standard procedure is to carefully intubate the opposite bronchus with a cuffed tube after a vigorous initial suctioning of all areas of the bronchial tree; this minimizes the spillover of contaminated secretions into less involved areas of the lungs. The patient is then placed in the face-down position and the thoracotomy and resection follow in a routine manner. There is usually a shortening of the bronchi as a result of the chronic inflammation present as well as increased vascularity and a proliferation of large perihilar and peribronchial lymph nodes.

Postoperative Management

To date 88 episodes have occurred in 46 patients.[2] Large doses of intravenous antibiotics are used, and early ambulation and introduction of physical therapy are urged. We do not recommend the use of intermittent positive pressure

TABLE 1

Pneumothorax in Cystic Fibrosis—Treatment

Initial	Further Treatment	No. Episodes	Resolved
None	—	2	0
Observation	None	26	21
Observation	Tube thoracotomy	5	4
Observation	Thoracentesis	1	1
Tube Thoracostomy	None	32	28
Tube Thoracostomy	Multiple chest tubes	9	8
Tube Thoracostomy	Multiple chest tubes and tracheostomy	2	1
Tube Thoracostomy	Multiple chest tubes and nitrogen mustard	1	1
Tube Thoracostomy	Multiple chest tubes and talc	1	0
Tube Thoracostomy	Multiple chest tubes and thoracentesis	1	1
Tube Thoracostomy	Suturing of thoracostomy site	1	1
Thoracentesis	None	1	1
Thoracentesis	Tube thoracostomy	3	3
Thoracentesis	Repeat thoracentesis	1	1

apparatus.

Pneumothorax

The majority of the patients with this pulmonary complication were treated by tube thoracotomy. This is usually done under local anesthesia if the patient is at all cooperative. Underwater seal and suction is used until there is no further evidence of air leakage and the lung is expanded as indicated by x-ray. The chest tube is then clamped for a 48-hour period and then removed if the lung continues expanded.

Our initial choice of treatment has depended on the clinical status of the patient and the degree of lung collapse (Table 1). Two patients expired before any treatment could be instituted, the pneumothoraces having occurred as terminal events. In 26 patients who had minor degrees of pneumothorax, no treatment was undertaken other than rest and observation. Four of these expired during hospitalization. In all the surviving cases the involved lung reexpanded. Six patients were initially followed by rest and observation alone, but soon required additional treatment due to increase in size of the pneumothorax. For 32 episodes, patients were treated with a single thoracostomy. An additional 15 cases were initially treated with a single chest tube, but further procedures were required for complications which ensued. Five patients were initially treated with thoracentesis, but four of these later required further procedures for re-accumulations of pleural air.

None of the cases have been treated with an open thoracotomy and stripping of the pleural surface. This is a subject to which we are giving considerable thought. In view of the high percentage of recurrences, it may prove advisable in certain selected patients to obliterate the pleural space and thereby prevent any future collapse.

A drawback of underwater seal suction and drainage is that the patient is relatively immobilized and thus at risk for accumulation of bronchial secretions. For milder degrees of pneumothorax and where there is no additional fluid to be removed, we are contemplating the use of the Heimlich one-way flutter valve.[3] This valve, which is attached to the end of the intrathoracic catheter, requires no suction, the air being expelled by the force of the patient's cough and forced increase of intrapleural pressure. The obvious advantage is that the patient can be fully ambulatory at all times.

Empyema

The standard surgical treatment for this complication is tube thoracotomy and drainage. Hopefully, this can be done without rib resection. Fortunately, empyema has become much less frequent in recent years, most likely because of early and massive antibiotic therapy for acute pulmonary infections.

Hemoptysis

Massive hemoptysis is occurring more frequently.[4] To date, we have not employed surgical intervention as the definitive means of controlling hemostasis. It is our opinion that the areas of bronchiectasis, from which the bleeding originates, have been too numerous and diffuse for resection. An additional difficulty has been the inability to precisely localize the site, not just the site of the bleeding. However, in view of the high mortality involved with massive hemoptysis, a more aggressive surgical approach may be justified in certain selected cases.

Results

Table 2 shows the findings in the 38 patients with cystic fibrosis who have been treated surgically. It is interesting to note that there were more than twice as many resections on the right side as on the left. The right upper and middle lobes were far more often involved than the lower. Since this does not hold true on the left side, it has been said that this distribution of localized atelectasis is reminiscent of the pattern likely to be seen in aspiration disease of the lung. In four of the 39 resections in these 38 patients, the underlying cause for the atelectasis was found to be botryomycosis. In five cases the atelectasis and bronchiectasis were so extensive that total pneumonectomy was required.

The results obtained in this group (Table 3) indicate that worthwhile palliation is possible in carefully selected patients. Twenty-four (62%) of the patients in this series obtained a good or excellent result. Eight (22%) had a poor or unsatisfactory result; in retrospect this was largely due to poor patient selection for surgery.

Conclusion

In the past, pulmonary surgery was felt by most to be contraindicated in this disease. We have shown by the above experience that there is a definite place for surgery in selected individuals. At present, such surgery is entirely palliative. The time may come when organ transplantation procedures will be well-enough developed so that lung replacement may be possible.

Acknowledgment

The majority of the operative procedures included in this report were performed by Dr. Samuel R. Schuster of our surgical staff.

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Diabetes Kills

In a recent study conducted at Joslin Clinic, Boston, the average duration of life after the onset of diabetes in the young was reported to be less than 30 years! The latter part of these years is usually associated with blindness, hypertension, renal failure and other serious disabling complications. Diabetes affects more than 70,000 Minnesotans. It is the third leading cause of blindness, and the seventh cause of death in the United States.

Diabetes cannot currently be cured but can be controlled. Optimal control, however, can be carried out only by a well-informed cooperative patient working closely with an interested physician.

Education is a vital part of medical care for a patient with diabetes and his family. Minnesota is fortunate in having an area resource center which can provide extensive patient and family education. The Diabetes Detection and Education Center is a unique program supported by the U.S. Public Health Community Health Grant and the Northlands Regional Medical Program. Physicians in this region can refer patients to the Center for a five-day (40 hour) intensive educational program in diabetes and its management. A minimal tuition is charged and a complete report is returned to the referring physician. If long-term complications associated with this disease are to be minimized and hopefully eliminated, then optimal control by informed patients must be initiated at the onset of the disease. It is hoped that the Diabetes Center can assist the practicing physicians in initiating this form of quality medical care. Further information regarding the program or patient registration may be acquired by writing or phoning the Diabetes Detection and Education Center, 916 East 15th Street, Minneapolis, Minnesota 55404. Phone: 332-2446.

A man of sixty has spent twenty years in bed and over three years in eating.— Arnold Bennett

Cystic Fibrosis[*]

A New Challenge to Internal Medicine

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In recent years curiosity concerning the natural history of cystic fibrosis has led to several analyses of the survival of patients with that disease. With the accumulation of data through a nation-wide data collection system and a research grant sponsored by the National Cystic Fibrosis Research Foundation, we have disclosed marked improvements in the survival of these patients. We can now predict that over one third of the patients with cystic fibrosis, who are receiving treatment at a Cystic Fibrosis Center, will survive to receive care from the physician who practices internal medicine. These data also indicate that, at present, patients with cystic fibrosis who reach age 20 have a significantly higher mortality rate than younger patients.

Survival Curves

Prior to 1939

The Figure illustrates survival curves of patients with cystic fibrosis who have received various types of therapy.[1] The curve labeled "pre-1939 cases" is a survival cure for all reported patients with cystic fibrosis diagnosed prior to 1938. The high mortality in the first year of life is clear, retrospective confirmation of the clinical impression of the early 1940s that cystic fibrosis was a fatal disease of infants.

Minnesota Curve before 1963

The curve labeled "Minnesota before 1963" is representative of half a dozen curves obtained from patients diagnosed and treated for cystic fibrosis prior to 1966. The patients in these groups received antibiotic therapy plus general supportive measures—vitamins, pancreatic enzymes, expectorants and anabolic agents. We have interpreted the improved survival to indicate that the survival of children with cystic fibrosis is significantly improved

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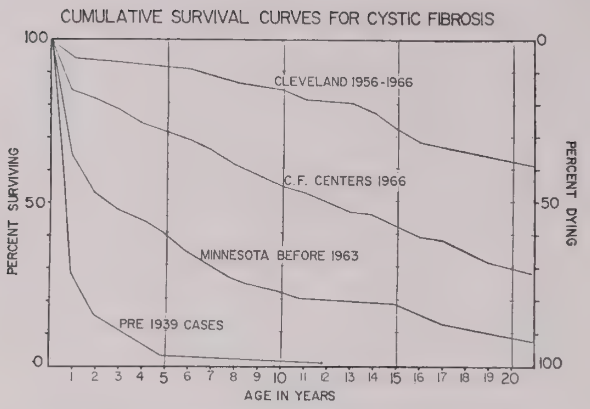

Figure—Life expectancy curves for the natural course of cystic fibrosis and the improved prognosis with antibiotics are compared to mist tent, face mask aerosol and physical therapy drainage. The curve for patients cared for in cystic fibrosis centers and cystic fibrosis clinics in 1966 is based on 4,048 patients who received all types of pulmonary therapy plus antibiotics and other medicines. The curve for Cleveland is based on prophylactic pulmonary therapy approach developed at Western Reserve University by Matthews and Doershuk.

when the infectious pulmonary complications are treated.

Cystic Fibrosis Centers 1966

The third curve labeled "C.F. Centers 1966" represents the survival for 4048 patients with cystic fibrosis seen in 1966 at thirty-six cystic fibrosis centers throughout the country. These patients received the same supportive therapy given to the patients treated in the second curve plus various types of pulmonary therapy, including aerosol by face mask and mist tent and physical therapy to remove secretions from the lungs. The method of prescription of these treatments varied considerably from one center to another. At some centers these pulmonary treatments were reserved for patients who had severe disease, at others for patients who had any pulmonary disease, and at a few for all patients whether or not they had pulmonary

TABLE I
Age Specific Mortality Rates for Patients With Cystic Fibrosis
1964, 1966, and 1967

Year of life	64		66		67		Age period
0-1	.1048		.1554		.0757		Infancy
1-2	.0405		.0254		.0322		
2-3	.0454		.0387		.0431		
3-4	.0428	—.0376*	.0521	—.0387*	.0323	—.0415*	Pre School
4-5	.0376		.0399		.0481		
5-6	.0361		.0318		.0444		
6-7	.0235		.0447		.0480		
7-8	.0675		.0706		.0571		
8-9	.0490		.0737		.0716		
9-10	.0743	—.0609*	.0583	—.0576*	.0608	—.0586*	Primary
10-11	.0290		.0442		.0615		
11-12	.0923		.0483		.0552		
12-13	.0538		.0510		.0454		
13-14	.0432		.0425		.0302		
14-15	.0709		.0333		.0612		
15-16	.0854	—.0521*	.0613	—.0554*	.1253	—.0715*	Secondary
16-17	.0235		.0241		.0511		
17-18	.0377		.1241		.1006		
18-19	....		.0714		.0608		
19-20	.2040		....		.1898		
20-21	.1538		.1043		.1667		
21-22	....	—.1812*	.0977	—.1205*	.1413	—.1861*	Post high school
22-23	.1379		.0910		.0556		
23-24	.2105		.1667		.1634		
24-25	.2000		.1429		.3000		

*Unweighted average age specific mortality rates.

disease. We have interpreted this improved survival as the direct result of the improvement in care which can be given by a physician who is knowledgeable in the disease and its complications and who adds the elements of pulmonary cleansing to the treatment program.

Cleveland 1956-1966

The fourth curve, "Cleveland 1956-1966," is data obtained from the Cystic Fibrosis Center at Case-Western Reserve University. All the patients at this center have been given the elements of therapy mentioned above, but the therapy has been used continuously from the time of diagnosis. This curve shows further significant improvement in the survival. We have interpreted this to indicate that the pulmonary complications of cystic fibrosis which lead to morbidity and death can be prevented or delayed by the early application of prophylactic pulmonary therapy.[2]

In comparing the curves we note four important findings: First, the period of greatest mortality is in the first year of life. Second, the more elements of therapy and the more intensely they are used, the greater the decrease in the first year of mortality. Third, the slope of the curve at the 50-percent survival decreases simultaneously with the availability of more techniques for therapy and with the great intensity in which these treatments are applied.

Fourth, in the curve with best survival, the slope increases as the age of the patient group increases, indicating an accelerated mortality with advancing age.

Mortality Related to Age

In Table 1 are recorded the age-specific mortality rates for patients with cystic fibrosis being treated at cystic fibrosis centers in 1964, 66, and 67. These data are based on all reported patients and include male and female patients unselected for birth complications. The data

TABLE 2

Age Specific Mortality Rates for Male and Female Patients Seen in 1966 and 1967

Year of life	All patients		Male		Female		Age period
0-1	.1176		.1153		.1199		Infancy
1-2	.0256	—.0438*	.0383	—.0347*	.0133	—.0528*	Pre school
2-3	.0454		.0190		.0703		
3-4	.0397		.0280		.0513		
4-5	.0539		.0384		.0692		
5-6	.0449		.0296		.0605		
6-7	.0536		.0549		.0523		
7-8	.0688	—.0656*	.0464	—.0565*	.0941	—.0737*	Primary
8-9	.0722		.0813		.0609		
9-10	.0786		.0642		.0791		
10-11	.0603		.0704		.0482		
11-12	.0566		.0336		.0833		
12-13	.0574		.0435		.0771		
13-14	.0478	—.0688*	.0534	—.0595*	.0405	—.0801*	Secondary
14-15	.0496		.0614		.0343		
15-16	.1009		.0938		.1099		
16-17	.0339		.0275		.0422		
17-18	.1048		.0659		.1481		
18-19	.0762		.0556		.1061		
19-20	.1378	—.1682*	.1243	—.0994*	.1552	—.2984*	Post high school
20-21	.1702		.1099		.2593		
21-22	.1297		.0800		.2143		
22-23	.1379		.0500		.3333		
23-24	.1840		.0506		.4286		
24-25	.2500		.1818		.4000		

*Unweighted average age specific mortality rates.

have been divided into five age periods.

Infancy

The first year of life because of the high infant mortality.

Preschool

The next six years of life, essentially the preschool period, during which an age specific mortality rate over 5 percent was observed only once. During this period the unweighted average age specific mortality rates for each of the years are close to 4 percent.

Primary

The six years of primary school during which we see a slight increase in the unweighted average age specific mortality to 6 percent per year.

Secondary

The six years corresponding to the junior and senior high school years during which the unweighted average age specific mortality rates underwent no essential change.

Post High School

The six years post high school encompasses ages 19 through 24. In a sense these patients are "on their own" and appear to do poorly. The unweighted average age specific mortality rates calculated for these years are two to three times greater than the rates of the previous two periods.

Mortality Related to Age and Sex

Table 2 contains the summarized data for the years 1966 and 1967, all patients seen, all males and all females. The five age periods are again used for comparing the survival of the males and females. This Table suggests that the male with cystic fibrosis has a survival advantage over the female. In the first year of life the evidence is slight, as the mortality rate for males is only slightly lower than for females. The rates are based on reports of 342 males and 353 females.

In each of the next three age periods, the preschool, the primary and the high-school periods, the mortality of the females is about 50 percent higher than the males. However, in the post-high-school period, the female mortality is 300 percent greater.

These mortality rates can be compared to a "base line," the preschool mortality, where we see a slight increment in mortality rates through each of the age periods: for males from 3½ to 5½ to 6% and then to 10%, a three-fold increase from the preschool to the post-high.

In contrast, for the females we find increments from 5 to 7 to 8 and then to 30 percent, a six-fold increase in mortality from the preschool to the post-high-school period and a three-and-one-half-fold increase in mortality from the high-school to the post-high-school period.

Discussion

The age-related increment in mortality from cystic fibrosis defies complete explanation. Nevertheless, we must analyze the possibilities so that we can attempt to change the course of these patients.

One obvious explanation is that these patients lived their early years prior to the general use of pulmonary therapies and, therefore, acquired such severe lung disease that these deaths in young adult life were ordained and predictable. Insofar as this is true, prompt diagnosis and treatment are the only measures available for amelioration of this trend.

Some age-related change in therapy could be contributory, e.g., separation from the home, loss of Crippled Children Services support for drugs and medical expenses, change of physician, changes in attitude towards life, e.g., failure to obtain employment, fear of losing employment because of illness, symptoms of illness, loss of time while visiting the doctor, inadequacies concerning marriage and raising a family, problems of earning enough to pay for medical expenses and still enjoy the fruits of their labors.

Whatever the reasons are for any individual young adult patient, all these reasons are important for the group. Every physician who supervises the health care of a young adult with cystic fibrosis should be aware that such multiple problems can adversely affect his patient; he ought to be sure in his knowledge of cystic fibrosis therapy through experience at a cystic fibrosis center; he must also analyze his patient's social, emotional, economic as well as medical problem and enlist by consultation or referral appropriate paramedical and social agencies and businesses to resolve these problems.

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When the Brain Sleeps

An amazing thing took place on the Leningrad Front during the war. In May 1943 a wounded soldier in a very grave condition was brought to a field hospital. He was instantly put on the operating table. The operation began. Just then his blood pressure dropped dangerously. And the surgeon decided to make a blood transfusion there and then, while the operation continued. But it turned out that the conserved blood of the desired second group had all been used up, and two of the doctors instantly gave their own blood. Their blood was also of the second group. Three hundred and fifty cc were taken from each doctor, and the resultant total of 700 cc, a very big dose for a single transfusion, was immediately transfused to the wounded soldier.

Both the operation and transfusion were successful. There were no complications. The patient was making good progress. A few days later his condition was wholly satisfactory, and he was to be evacuated to the rear. But he looked pale and anemic, and the doctors decided to make one more blood transfusion. They took a blood test to make sure of his group, this being laid down by the regulations for each transfusion, and were aghast with the result. They could not believe their eyes. The soldier, it developed, belonged to the third-blood group, and not the second. Yet on the operating table no less than 700 grams of second-group blood had been transfused into him.

Seven hundred grams of second-group blood is certain death to a man with third-group blood. It is not surprising, therefore, that the doctors were utterly confused. The patient had not suffered any discomforts. On the contrary, the transfusion was followed by a marked improvement. For some reason incompatible blood had produced good results.

In 1943 the surgeons at the field hospital could not understand this phenomenon. But in 1944 it began to make sense. The remarkable and unexpected findings of Professor Galkin, a Leningrad patho-physiologist, and his associates shed light on the case when they discovered an amazing phenomenon: Many properties of the organism undergo great changes under the effects of narcotic sleep. Anesthetized cells can live under conditions that would be fatal to them under ordinary circumstances*

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*L. Fridland, M.D.: The Achievement of Soviet Medicine, Edited by W. Horsley Gantt, M.D., 1961.

Editor's Note: Transfusion with incompatible blood is not a safe procedure under any circumstance and can never be recommended.

His handshake ought not to be used except as a tourniquet.—Margaret Halsey

Social Stigmata of Cystic Fibrosis*

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INHERENT IN THE physician is the desire to heal and restore his patients to normalcy. Often the medication that one prescribes becomes a magic potion to relieve the doctor's anxiety as much as to provide therapy for the patient. Because the emotional need of the physician is normally met by those acute medical and surgical problems which respond to immediate treatment, it is understandable that the failure of a patient with a chronic disease to respond and to recover engenders frustration and even annoyance. As a result, very few physicians find themselves attracted to treating chronic and prolonged illnesses, let alone those which can never be cured.

Likewise the relatives and parents of a chronically ill child find themselves annoyed, fatigued, and emotionally exhausted by the demands placed upon them to alleviate the illness. "Doctor, surely you or we can do something" is a plea that often expresses the sharing of the physician's inability to produce a cure.

The public renders sympathy and compassion for a crippling or chronic disease where a limp, a crutch or a brace is the symbol of an illness. The understanding that the patient and relatives receive from others observing such a handicapped child alleviates to some degree the burden by partial identification with the patient. But a child handicapped by a chronic disease which lacks such symbols receives very little empathy from the general public. In the case of cystic fibrosis the unglamorous association of foul-smelling stools, thinness, chronic cough and even disgusting purulent sputum produces a certain amount of annoyance or even loathing.

The empathetic pediatrician has learned that when a child has a prolonged illness which will result eventually in death and is accompanied by suffering for both the patient and the parents, a time arrives when the parents, exhausted by the medical treatment and the heroics, accept the inevitable death more realistically. Frequently the child recovers sufficiently to be discharged from the hospital to return home to await the next exacerbation of the disease. A point is finally reached in which the remissions may understandably be almost resented by the parents, for it is only normal that they should look forward to the relief of the patient's suffering by death. It takes a brave and intelligent parent to say openly, "I hope that my child does not suffer too much longer," and to realize that he may be expressing his own desire to be relieved of "chronic sorrow." I would suspect that the clergy and the physician, by not comprehending or recognizing the unspoken wish, are creating more guilt than is society by its silent censure.

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*Read at the Regional Continuation Course on Chronic Respiratory Diseases in Children and Adolescents at the University of Minnesota, Minneapolis, September 17, 1968.

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While we of the medical team must not give artificial hope, we must recognize that it is our duty as skilled, specialized pediatricians to produce a remission and restore the child to relative normalcy of living. We all have seen young adolescent cystic fibrosis patients who many years previously we had felt had but a few months to live. When one considers the medical and lay anticipation of a miracle to be found in a cure for such an entity as leukemia in childhood, where intensive therapy and hope is extended for a period of six to twelve months, we should be mindful of the years we have in our favor to reach ultimate control of cystic fibrosis.

The interpersonal relationships of a small child with cystic fibrosis may be perfectly normal when the child has been followed in a suitable clinic or center and is receiving the optimum therapy without incapacitation. However, when the condition has so progressed as to disallow normal exercise and social group activities, nothing is sadder to observe than the loneliness of a child looking out from the inside of a home at other children laughing, running and playing.

As the child with chronic lung disease such as cystic fibrosis reaches adolescence the innate desire to rebel and flee from parental supervision and to become like his peer group is an instinctual drive. The adolescent does not want to be different from his peers but does want to be different from "the older generation." For the first time, parents may be aware that their young child is now ashamed of his affliction and may literally deny his illness and offer excuses for the cough, the clubbed fingers, or the inability to participate in rugged dancing or sports.

When one recognizes the adolescent struggle for identity and acceptance both by himself and by others, one need not be a sympathetic individual to recognize the added burden placed upon a chronically ill child. The third cause of death of fifteen-to-nineteen-year-old youths, especially boys, is suicide. These are youths who have not become social dropouts but rather life dropouts overwhelmed by the cynical hopelessness of living. It is understandable that the intelligent adolescent soon recognizes that he has an incurable disease and that either his siblings or other patients attending the same doctor's clinic have died from this illness. One can recognize the refusal of the adolescent to receive or give himself the necessary therapy, as a reaction to any of the many complex emotional adjustments required either within the family constellation or within the social group, or because of the hopelessness he may feel.

When this adolescent has conquered the trying periods of high school, rehabilitation programs, and/or college and is ready to obtain employment, he unfortunately may find the employer "does not wish to assume the risk of his employment." With the publicity and encouragement given to employers to hire the mentally and physically handicapped, many are anxious to hire such individuals as tokens of open acceptance by their personnel department; but there has been a marked delay in acceptance of cystic fibrotics. Many patients have found that they need to deny their disease in order to obtain employment. The insurance companies have been the target for alibis by personnel managers who say that employing cystic fibrosis individuals would raise the cost of their premiums and not meet the guide-lines set down by the insurance companies. Most of the insurance companies that the author has approached, however, have denied this. We are now at the point of requiring governmental decision and policy in this matter.

It has been the experience of the National Cystic Fibrosis Research Foundation that a clinic or center for the chronic pulmonary-diseased child needs to revolve around a dedicated, sympathetic pediatrician who is willing to serve as physician, confidant, social worker, psychiatrist, physiologist, and "Big Daddy" to the entire family of the child. It is dismaying and discouraging to note that many of the directors of clinics for handicapped children find their patients, their clinic and their efforts receiving so little acceptance by their hospital and school administration that they must fight for funds, space and understanding, just as the parents of these children have been doing for years.

On Prognosis

It appears to me a most excellent thing for the physician to cultivate Prognosis . . . He should observe thus in acute diseases: first, the countenance of the patient. if it be like those of persons in health, and more so, if like itself, for this is the best of all; whereas the most opposite to it is the worst, such as the following; a sharp nose, hollow eyes, collapsed temples; the ears cold, contracted, and their lobes turned out: the skin about the forehead being rough, distended, and parched; the color of the whole face being green, black, livid, or lead-colored. If the countenance be such at the commencement of the disease, and if this cannot be accounted for from the other symptoms, inquiry must be made whether the patient has long wanted sleep; whether his bowels have been very loose; and whether he has suffered from want of food; and if any of these causes be confessed to, the danger is to be reckoned so far less; and it becomes obvious, in the course of a day and a night, whether or not the appearance of the countenance proceeded from these causes. But if none of these be said to exist, and if the symptoms do not subside in the aforesaid time, it is to be known for certain that death is at hand.

And, also, if the disease be in a more advanced stage either on the third or fourth day, and the countenance be such, the same inquiries as formerly directed are to be made, and the other symptoms are to be noted, those in the whole countenance, those on the body, and those in the eyes; for if they shun light, or weep involuntarily, or squint, or if the one be less than the other, of if the white of them be red, livid, or has black veins in it; if there be a gum upon the eyes, if they are restless, protruding, or are become very hollow; and if the countenance be squalid and dark, or the color of the whole face be changed—all these are to be reckoned bad and fatal symptoms.

The physician should also observe the appearance of the eyes from below the eyelids in sleep; for when a portion of the white appears, owing to the eyelids not being closed together, and when this is not connected with diarrhoea or purgation from medicine, or when the patient does not sleep thus from habit, it is to be reckoned an unfavorable and very deadly symptom; but if the eyelid be contracted, livid, or pale, or also the lip, or nose, along with some of the other symptoms, one may know for certain that death is close at hand. It is a mortal symptom, also, when the lips are relaxed, pendent, cold, and blanched.*

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*Hippocrates: The Book of Prognostics

No National Boundaries

The great republic of medicine knows and has known no national boundaries.—Osler

Psychiatric Aspects of Chronic Lung Disease*

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EVERY PATIENT who visits a physician because he is ill is worried. This worry may institute a psychological regression in the patient which can vary from mild in a relatively well person to severe in a relatively disturbed person. This response to illness is an example of the general human response to external threat or disharmony with the environment. The physician's ability to understand how the anxiety associated with an illness affects the patient and to use this understanding in the medical management of a disease may be crucial.

One thing common to all patients is anxiety connected with the diagnosis of their condition. They cannot deny the threat of this illness, though they may try very hard to do so. Whatever conceptions or misconceptions they may have about what is necessary for treatment of their disease seem to increase their anxiety and tension. But what is important is that each of them reacts to the anxiety with ritual methods and attitudes. These behavior patterns have to be understood as part of the patient's personality. They represent his leading reactions to stress and are the result of a long history of adjustment. As he grows up with these constitutional endowments and environmental experiences, he learns to find ways to compromise between his need and wishes on the one hand and the prohibition against fulfilling them at any price and at every moment on the other. If these conflicts between impulses and control arrive at a certain equilibrium in the adjustment process, the results appear as personality traits. In times of increased conflicts, as under pressures of anxiety, personality characteristics increase in intensity, as they attempt to maintain the inner balance. The patient therefore becomes less manageable than under average life conditions. One must therefore ask not so much what one can request from the patient, but what can one do to help him overcome his emotional response so that he can accept his physician's recommendations.

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Case History

The patient is a 27-year-old man who was diagnosed as having cystic fibrosis at five years of age. Until the last few years he struggled with the feeling that his major identity was as a medical wonder, "one in a million," a "remarkable case." These labels connoted no sense of value or worth to him, only a sense of isolation, difference and aloneness. In addition, the medical procedures and equipment needed to maintain his functioning were hinderances to his wish for a sense of wholeness and adequacy. His feeling of defectiveness was even more stressful in the social area, where he could never be as active or as skillful as his peers.

Development and maturation is difficult enough without the added burden of limited opportunity with which to explore, test, and evaluate one's effectiveness as a person.

As a youngster, the patient was watched over and guarded by adults who were oriented to the possibility of imminent death. He was usually avoided by peers and potential friends who would "take a step back" upon learning that he had a serious illness. Teachers from grade school through college were reluctant to make demands or encourage long-range tasks which might prove stressful or be abruptly terminated by death.

These attitudes of others toward illness and death were always difficult for him to deal with until he became better able to cope with his own. Rather than confront people and ask for clarification of their ideas about his situation, he would withdraw. He became hesitant to involve himself with others because of his anxieties about exposing his feelings regarding the implications of his grave medical problem.

Several times in his life he had felt that psychiatric help would be quite useful in learning to cope with, not only his medical problem, but the everyday problems of living as well. As a youngster, he would probably have benefited most from intervention directed toward helping his parents to deal with his anxieties and questions as well as their own, and to develop more appropriate expectations of achievement and activity.

Later in the patient's life he often wondered about seeking psychiatric aid by sorting out his feelings in an effort to become a more effective person, but this idea was as disconcerting to him as it is to most people. He was unsuccessful in pursuing this idea as he could not come to any decision as to what problem to seek help for. The medical problem was being effectively handled by his physician, and he was uncertain whether his vague depression and anxieties were appropriate to take to a psychiatrist.

Even when he was seen by a counselor in college, he found it difficult to describe his needs and guide the therapist toward his areas of discomfort. The therapist in turn tended to be more concerned about his illness, following the pattern of seeing him primarily as a sick person.

It was not until two years ago at University Hospitals that doctors helped him enlarge this self image of a seriously ill person to a man with a serious illness, a shift of attitude which proved successful in all areas of his life. Through the encouragement to broaden his horizons and to persevere in looking for a job, he found hope that he could be a useful human being.

He had graduated from college with a degree in art but had been unsuccessful in gaining employment in this area as well as in others. Interviewers had not asked for clarification of his medical status but had only to hear that he had a chronic illness to refuse his applications. With the support of his doctors and the staff of the Cystic Fibrosis Foundation, the patient continued to look for work without denying his illness and without completely giving up hope of employment. He was finally hired in a managerial capacity with a major music distribution and retail firm where his drive to succeed has carried him quite rapidly into additional areas of responsibility. In this position he has been able to use his artistic talents and his growing skill in working with others.

Comments

Having given up a death orientation and taken on a new commitment to living the patient also decided to marry. He recently married a nurse from University Hospitals whom he met two years ago while hospitalized there.

They have decided not to have their own children but will attempt to adopt some. The decision to marry and raise a family was not taken lightly by either him or his wife. They were aware that many people would consider it unrealistic; indeed a most painful illustration of this involved his mother-in-law. When they visited this woman she was quite open and warm in receiving him as a son-in-law, but as the visit wore on she became more honest about her anger: in their marrying there was, in her opinion, a very high probability of early widowhood for her daughter and early death for any children they might bring into the world. He allowed her to vent her ire, thereby tapping his own concern, and was then able calmly and non-defensively to explain their reasons for going ahead.

A new-found confidence and strength in dealing with himself and others has led to a much more rewarding life. He denies neither the threat of death nor the reality of being alive. The impact of his present commitment to living is best illustrated by a relative who recently remarked, "Why L——, I remember you when you were dying!"

Summary

Chronicity can not only become a way of life for a patient; it also has the ability to evoke many reactions from those who are associated with him or who provide necessary care and treatment. The word carries a gloomy connotation and probably should never be used in discussing illness with a patient, for the person who hears his illness described as chronic may consider it beyond hope or help. For this patient, the concept of chronic disease had significant psychologic and social ramifications.

These principles apply to decisions around dietary restrictions and various forms of rehabilitation connected with chronic lung diseases. Whatever measures have to be instituted, in terms of the various forms of rehabilitation connected with chronic lung diseases, the gain from understanding the patient's personality structure and his dominant, central emotional needs is considerable, since it will permit the physician to deal with the patient's problem in a more appropriate and positive form.

Shakespeare's Doctors

Cerimon

"'Tis known, I ever
Have studied physic, through which secret art,
By turning o'er authorities I have,
Together with my practice, made familiar
To me and to my aid the blest infusions
That dwell in vegetives, in metal stones;
And I can speak of the disturbances
That nature works, and of her cures; which doth give me
A more content in course of true delight
Than to be thirsty after tottering honor,
Or tie my treasure up in silken bags,
To please the fool and death." (Pericles III, 2)

Scornful of hollow prestige and venality, thus spoke Cerimon when his friends expressed surprise that he, a nobleman, should show an interest and some skill in medicine. While only an amateur rather than a certified physician, he fully qualifies as one of Shakespeare's doctors, acquitting himself as ably as any.

When a chest containing the "corpse" of Thaisa is cast ashore from a shipwreck off the coast of Ephesus and is opened, Cerimon immediately detects that the body within shows faint signs of life and sets about to revive it.

"For look how fresh she looks! Make a fire within:
Fetch hither all my boxes in my closet.
Death may usurp on nature many hours,
And yet the fire of life kindle again
The o'erpressed spirits.
The fire and cloths.
The music there!—I pray you, give her air." (Pericles III, 3)

Cerimon's arsenal consisted of warm packs, fresh air, stimulating music, and unidentified substances from his boxes, presumably stimulants.

When Thaisa finally stirs and murmurs, Cerimon orders her carried off to bed—to be watched over closely.

"Hush, my gentle neighbors!
Lend me your hands; to the next chamber bear her.
Get linen: now this matter must be looked to,
For her relapse is mortal. Come, come;
And Esculapius guide us!" (Pericles III, 3)

Subclinical Pulmonary Disease in Children*

An Exercise in "Subclinical" Logic

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VERY LITTLE HAS been written about "subclinical pulmonary disease" in children. Nevertheless, that phrase directs the mind into new channels, some of which will be explored here. Perhaps a crude map of this Terra Incognita will emerge.

We should begin with the key word itself. "Subclinical" is one of those etymological horrors that combines words from two languages. "Sub," of course, is Latin and means "under," whereas "clinical" comes from the Greek ϰλινιϰσς or "bed." It is mildly ironic that the clinic is a patient-care area that almost never contains beds. Subclinical therefore means "under the bed," which suggests dust, last Sunday's *Times*, or a chamber pot. But is there a better word? Could one use "asymptomatic?" I think not, since one can be asymptomatic either with or without disease. Moreover, clinical diagnostic methodology may detect disease that is asymptomatic—that is without symptoms. We shall stick with "subclinical" and develop its meaning by usage, since its derivation is not helpful.

Most physicians use the term "subclinical" to mean that disease exists in a patient in the absence of both signs and symptoms. Since the organs in question here are the lungs, subclinical pulmonary disease would imply disease of the lungs in the absence of cough, chest pain, dyspnea, bronchial breath sounds, etc.

Pulmonary diseases can be divided into subheadings of acute and chronic, as exemplified by pneumococcal pneumonia and tuberculosis. Can one speak of subclinical *acute* pulmonary disease? Undoubtedly it exists, but, as a practical matter, one can question its importance. If a disease is progressing rapidly, it will soon surface and become "clinical." If it goes away, what difference does it make? Our concern here is clearly with subclinical *chronic* pulmonary disease.

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Read at the Regional Continuation Course on Chronic Respiratory Diseases in Children and Adolescents at the University of Minnesota, Minneapolis, September 17, 1968.

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A definition is badly needed of "chronic pulmonary disease." I shall not attempt one here but, like you, will be thinking of protracted diseases affecting the lungs of children—tuberculosis, cystic fibrosis, fungous infections, sarcoidosis, and many others, including asthma.

Set theory and the Venn diagram can be used to explore subclinical disease of children's lungs. In the use of such diagrams, one must start with a Universe. Our Universe is depicted as a rectangular figure (*A*) that encloses "all children." Within the Universe are well children, sick children, children with chronic pulmonary disease, children without chronic pulmonary disease—literally, all children. The Universe is in flux since it is constantly being expanded by birth and contracted by death and graduation to adulthood (*B*).

Within our rectangular Universe we can define a circular "set," that is, a group of children differing in some respect from all other children. Set I represents children seen more or less regularly by doctors (*C*). Obviously, those within the Universe and outside of the set are not being so examined.

Clinical Disease

We can define another set. Set II shall consist of children with clinical pulmonary disease (*D*). They cough, produce sputum or blood, run fever, flare their alae nasi, and do all those things that one classically associates with diseases of the lungs. The majority of these children would be seen by a doctor; therefore Set II is mostly inside of Set I. However, for any of a thousand reasons, some would not be seen by a doctor and thus are represented by the portion of Set II that falls outside of Set I.

"False" Subclinical Disease

Another set, Set III, can now be developed within the Universe. It can be called "false" subclinical disease, whereby we indicate a group of children with mild or subtle expressions of their pulmonary disease (*E*). This group might be easily missed by a rushed history or superficial physical examination. But it would be detected by careful history-taking techniques or quantitative approaches to the physical examination. If it is true that the physician himself has trouble recognizing false subclinical disease, so indeed will the parent. Perhaps the majority of these children will not be taken to the doctor's office. Therefore Set III will lie to a greater extent outside of Set I than will Set II.

"True" Subclinical Disease

There is still another group within the Universe that is composed of children with pulmonary disease with absolutely no sign or symptom of its presence. They are diagnosable by application of a test—a tuberculin or sweat test, for example. This Set IV overlaps Set I only to the extent that chance alone will bring its members to a doctor's office (*F*). Furthermore, children within this set will be identified by the physician only if he does the right screening test.

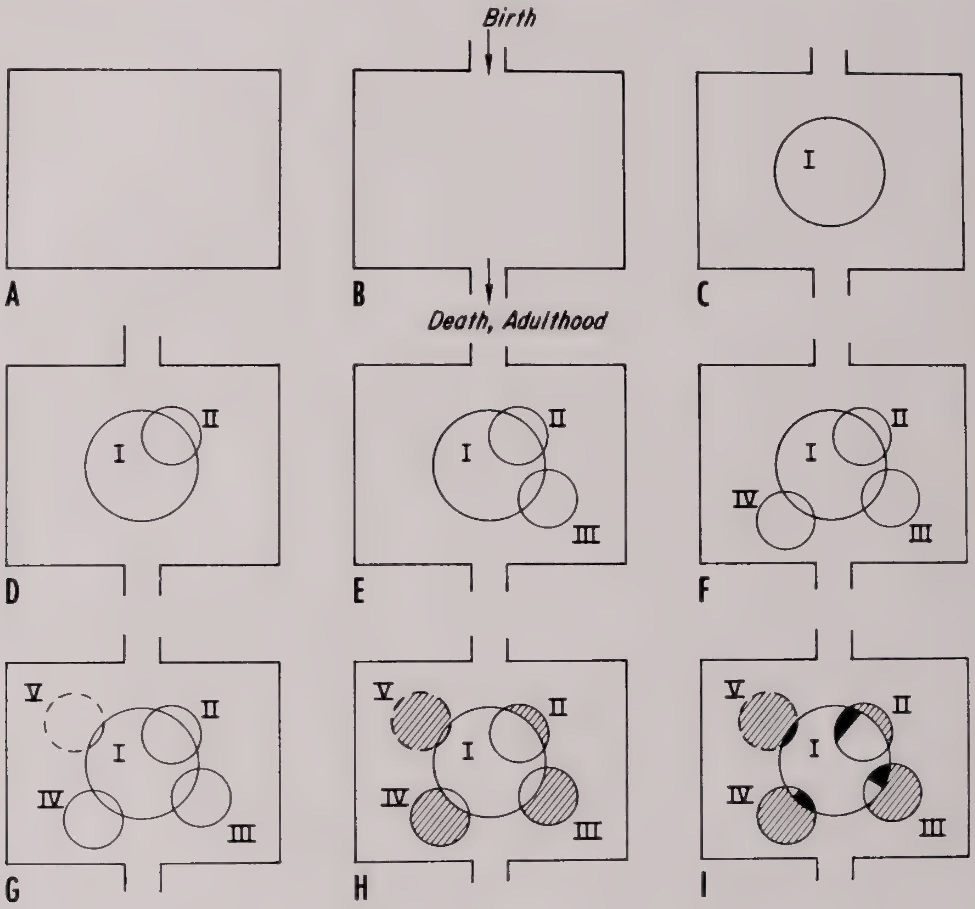
There is a last set, also of "true" subclinical disease, but in this case there exists no test that will identify its members. Set V, then, is undiagnosable true subclinical pulmonary disease. Its nebulosity is indicated by dotted lines (*G*), and its unidentifiable members float in the Universe and are seen by a physician for reasons other than their pulmonary disease. How do we know that such a set exists? It must exist. There is surely some molecular, biochemical, or biological deviation from normal that exists for a variable period in the natural history of any disease before conventional tests become positive and long before symptoms or signs appear. How does one diagnose primary pulmonary tuberculosis in the weeks between initial infection and the development of a cutaneous response to a tuberculin test? How does one recognize the "disease" produced in an asymptomatic adolescent cigarette smoker? Pulmonary function testing is scarcely the answer.

We have now diagrammed all possible categories of chronic pulmonary disease. It should be obvious that every child falling outside of Sets II through V does not have chronic pulmonary disease.

The relationship of the four disease sets to Set I is of interest. It is clear that, as disease becomes increasingly symptomatic, the chances of diagnosis are increased. The cloudiness of Set V, which has little in common with Set I, and the large overlap of Sets I and II represent the extremes of potential disease recognition by the physician.

The fully developed Venn diagram can now be used to define the children with pulmonary disease who will *not* be diagnosed. Clearly, those portions of each of the four disease sets that do not overlap Set I will not be recognized because the physician has no contact with the patient (*H*, shaded portions). But others will not be diagnosed either. Will a physician make an accurate diagnosis of every patient with obvious clinical disease? Humility and our own past experience tell us that some obvious diagnoses will be missed, even by competent clinicians. This percentage of missed diagnoses must increase as the difficulties of possible diagnosis increase. Ultimately, in no patients of Set V that the physician may see by chance will a correct diagnosis be made. Thus, even within his sphere of influence, the doctor will overlook children with chronic pulmonary disease (*I*, black portions).

Our Universe is in flux (*B*) due to children constantly both entering and leaving it. So too are the sets within the Universe. As a disease progresses, a child may move from Set V to



Figure

Venn diagram of clinical and subclinical chronic pulmonary disease. *A:* rectangle comprises *all* children (the Universe); *B:* the Universe is in flux, expanded by birth and contracted by death and adulthood; *C:* Set I comprises those children examined by a physician; *D:* Set II comprises those children with clinical pulmonary disease who may or may not be seen by a physician; *E:* Set III comprises those children with subtly expressed clinical pulmonary disease ("false" subclinical); *F:* Set IV comprises those children with no clinical expression of pulmonary disease, that is nevertheless detectable by application of the proper screening test (diagnosable "true" subclinical); *G:* Set V comprises those children with no clinical expression of pulmonary disease that is not presently detectable by any test (undiagnosable "true" sublinical); *H:* Analysis of types of pulmonary diseases that will not be recognized because of lack of exposure to the physician or to absence of a proper screening test (shaded portions of sets) and also because of diagnostic failure by the physician (black portions of sets). See text for further exposition of the diagram.

Set IV to Set III, standing more of a chance all the time of being one of those lucky individuals seen by a doctor who makes the correct diagnosis. It is also apparent that a self-limiting disease may be charted as retracing its steps back through the milder sets and finally into the pulmonary disease-free Universe.

The Venn diagram, as developed thus far, has been qualitative only—a model for consideration of diagnostic feasibilities. It shall remain qualitative here; but such a portrayal begs for quantitation in which the sizes of the sets would roughly portray the number of children represented by each. The Venn diagram would be different for each disease, depending on its incidence, symptomatic expression, and test-specificity. The spectrum of chronic pulmonary diseases then would consist of a spectrum of Venn diagrams, the area of whose black or shaded portions would indicate where diagnostic action must be taken. Therapeutic advances would be limited to the "white" portions of a diagram within Set I.

Efforts to increase the recognition of chronic pulmonary disease can be divided into those falling within Set I (the physician's sphere) and those outside of Set I (the community's sphere).

Improved Disease Recognition by the Physician

A physician can do little about those children with true subclinical disease for which no test is available. He can only await the discovery of new tests through the channel of basic and clinical research. Perhaps he can do more in the area of true subclinical disease for which tests are available (Set IV). Since the child is asymptomatic, the physician should apply certain screening tests to his entire patient population. The tuberculin test is a good example, since it is still not being universally and systematically used by physicians. Unfortunately, there is as yet no accurate screening test for cystic fibrosis that can be used in the doctor's office. Testing for cystic fibrosis is still being done only on patients in Sets II and III, although the future looks bright for such a test.

Every doctor should be interested in increasing his diagnostic efficiency in the areas of Sets II and III. Two of the purposes of a regional course such as this are to increase awareness and refine conventional diagnostic methods.

Certain non-specific screening tests are open to the physician. These include the chest x-ray, office pulmonary function testing, and office testing of immunologic competence. If, when, and how such testing should be routinely done remain to be decided. A chest x-ray in the newborn nursery prior to discharge does not seem unreasonable. Such a screen would undoubtedly pick up infants with congenital pulmonary or cardiac disease that would otherwise be missed. Routine testing of peak expiratory flow rate is easily introduced into a busy pediatrician's office for children older than four years. A child with peak flow more than two standard deviations below the mean for his height could then be more carefully evaluated. The competence of the humoral antibody system could be tested by a Schick test after routine DPT immunization. These are a few examples of simple diagnostic methods now available for the early detection of treatable pulmonary disease.

We must now consider the possible detection of chronic pulmonary disease outside of Set I, and thus outside of the direct control of the physician. This is clearly the community's area of activity. Increased recognition here must depend on the physician-citizen and on both governmental and private organizations whose mission is the eradication of pulmonary disease. We must include the Division of Chronic Disease Programs, the Division of Regional Medical Programs, the National Institutes of Health, state and city departments of health, the American Academy of Pediatrics, the National Tuberculosis and Respiratory Disease Association, the National Cystic Fibrosis Research Foundation, the American College of Chest Physicians, and others. From one or more of these groups must come the concept, development, and subsequent field trials of the necessary community-wide screening tests.

The problem boils down to a selection of diseases to test for, and this selection in turn depends on a number of factors, such as the nature of the disease, its incidence, its mortality, its morbidity, and its inertia. By the term "inertia" we mean the qualities of acceleration and momentum. Does a disease move rapidly and end quickly (low inertia) or does it start slowly, gain momentum, and end slowly (high inertia)? Diseases of high inertia usually have prolonged periods of true subclinical expression.

Another factor in selecting a disease to screen for would be the expected gains of early recognition. Obviously, both the community and the individual gain from early recognition of tuberculosis. It has been shown that the early recognition of cystic fibrosis is associated with increased longevity, because treatment of a preventive nature can be employed before considerable pulmonary destruction has occurred. Early recognition must have a tangible "pay-off."

The state of the art in screening for a disease must be examined. Is a test available, and, if so, is it cheap, brief, simple, painless, specific, objective, accurate, and precise?

There is no simple approach to the recognition of subclinical pulmonary disease in children. It will depend in part on the development of a bona fide pediatric subspecialty of pulmonary disease. The impetus must come from the pediatrician, regardless of whether he is acting as an individual or within a group.

A reasonable step at this time would be the establishment of a Task Force to study the problem, including defining and listing the various diseases, outlining what is known of their incidence, clinical expression, recognition, and treatment. Such a Task Force, supported by some or all of the interested groups above, could then set priorities for action. Its opinions, published and widely circulated, could serve as documentation for requests to foundations and governmental bodies. After all, the logic of the Venn diagram suggests that the children in the "white" parts of the pulmonary disease sets must first be recognized in order to be treated.

Steven Strong, M.D.

There's little to say about me concerning the September cover photo except that I'm a "struggling" medical resident at the Veterans Hospital. I'll be on Uncle Sam's "war(d)" in a year, and so I'm watching the "Viet(al)" signs . . . (heh heh . . . and Viet Nam suffers from "gram-negative" (red) infiltration . . . mili(t)ary disease . . . and chronic (Tet)perature attacks . . . and all we need is . . . oh you guessed . . . chronic Am(peace)cillin!

The photo was taken during a tour of the National Parks with an old Argus, $300 and a wrinkle-nosed VW.

Keep Hammering

A professor of law said to his students: "When you're fighting a case, if you have the facts on your side, hammer them into the jury, and if you have the law on your side, hammer it into the judge."

"But if you have neither the facts nor the law?" asked one listener.

"Then," answered the professor, "hammer the table."*

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*Maxwell Droke: The Speaker's Handbook of Humor.

Knowledge

If the average person were credited with what he knows and charged with what he thinks he knows but doesn't, he most likely would be rather heavily in debt.

Onions can make even heirs and widows weep.—Benjamin Franklin.

Respiratory Complications of Cystic Fibrosis*

Prevention

WARREN J. WARWICK, M.D.†
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If the pulmonary complications of cystic fibrosis constitute the most severe and malignant pulmonary disease in childhood, causing premature deaths in affected children, and if the pulmonary complications are preventable, we have the basis for a comprehensive preventive medical program.

Six reports of the survival of children with cystic fibrosis not receiving special pulmonary therapies showed first-year mortalities of 33 to 65 percent.[1] The best of these series showed a 50 percent mortality by three and a half years and 90+ percent mortality by 20 years.

Cumulative data from the National Cystic Fibrosis Research Foundation Centers from 1966 to 1967 showed a mortality of 11 percent by age one, and 80 percent by age 20.[2] Cumulative data from the Center at Case-Western Reserve School of Medicine, 1958-1967, showed a 6 percent mortality at age one year and 38 percent at 20 years.[3]

These data clearly indicate that therapy now available can greatly alter the course of cystic fibrosis. But what is the best time to start such therapy?

Shwachman and coworkers reported their experience with infants with cystic fibrosis diagnosed in the first four months of life, eliminating infants with meconium ileus. When their data are compared with the National Cystic Fibrosis Research Foundation Center patients without meconium ileus, we see a decrease in first-year mortality from 8 percent to less than 1 percent for patients with mild or absent lung diseases.

The decreased mortality is also obvious at 10 years of age when the comparative cumulative mortality for the two groups has reached 16 and 8 percent.

Matthews, Doershuk, and coworkers from Case-Western Reserve University had 65 patients in their series who were also diagnosed prior to four months of age. These data include infants with meconium ileus and, because of the small number, no division was made concerning severity of pulmonary complications. When the mortality for this group is compared to the mortality for the whole group of patients treated at that Center, we observe a decrease of first-year mortality from 6 to 4 percent and no deaths after six months of age despite over 200 followup years to ages up to 11 years.[3]

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*Read at the Regional Continuation Course on Chronic Respiratory Diseases in Children and Adolescents at the University of Minnesota, Minneapolis, September 17, 1968.

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Early Diagnosis

These analyses show that the mortality from the pulmonary complication can be reduced maximally by early diagnosis and intensive treatment beginning at the time of diagnosis. The tools presently in the hands of physicians in practice are a keen sense of suspicion and the sweat test. The physician convinced of the malignant nature of the pulmonary complications of cystic fibrosis and of the benefits of prophylactic pulmonary therapy will order at least two sweat tests on any infant with any of the symptoms in the Table.

TABLE

*Symptoms Suggestive of Cystic Fibrosis.

- Persistent cough
- Recurrent pneumonia
- Atelectasis
- Emphysema
- Asthma
- Hemorrhagic tendency
- Failure to gain
- Steatorrhea
- Jaundice
- Low salt syndrome
- A sibling with cystic fibrosis
- Vitamin A deficiency
- Meconium ileus
- Intestinal obstruction
- Rectal prolapse
- Edema
- Salty skin

However, adequate as such a program of sweat-testing every suspected child could be, the data of Shwachman[4] et al. and of Matthews, Doershuk, and coworkers[3] show that severe, even fatal, pulmonary complications can develop within a few months after birth. Therefore, in order to make the diagnosis before pulmonary complications have begun, physicians will have to develop tests which will be effective in the newborn nursery.

Screening Tests

Three possible newborn nursery screening tests for cystic fibrosis were the leading subjects at a recent National Cystic Fibrosis Research Foundation Center Directors Conference.[5]

One of these, the measurement of the albumin content of meconium has failed to live up to expectations and is now not recommended.

Nail Clippings

The use of neutron activation of the sodium, potassium, and chloride present in nail clippings is being studied at Baylor University, Houston, Texas,[6] and at Children's Orthopedic Hospital and Medical Center, Seattle, Washington.[7] This technique, still in development, excites high hopes because the analytical process can be automated and because, if the test can be made practicable and efficient, sufficient neutron activators exist to analyze nail clippings from every infant born in the United States. However, the state of art is such that false-positive and false-negative results are obtained over 10 percent of the time.

Sweat Test

Sweat-testing with a chloride specific ion electrode has, according to Dr. C. T. Gillespie, reached the stage of feasibility testing. He has proven the technique in a survey of 36,000 children up to age 18 years on Prince Edward Island in 1967. Later in 1967 in a three-month trial of newborn testing in Halifax, Nova Scotia, he found one newborn with cystic fibrosis in the first 300 tested.[5]

Comments

Large-scale feasibility testing of this technique is presently hampered by non-standardized equipment. The current best combination of equipment is the Orion specific ion meter Model 401, the Beckman chloride specific ion electrode Research Model 78527V, the Hydrocollator gel pack heating system, and the Temp block module heater.[8]

When neutron activation analysis of nail clippings or the chloride ion electrode sweat test or another technique makes newborn testing practicable, an estimated 3000 to 4000 new patients will be diagnosed every year. This large number will cause at least two problems. First, application of preventive treatment measures to such a large number of patients is beyond the capability of present cystic fibrosis centers for more than a few years; therefore in most cases care will have to be given by physicians outside of a cystic fibrosis center.

Second, the demands of the present techniques of prophylactic pulmonary therapy are unacceptable to some physicians; hence our present best treatments may not be generally used by all physicians.

However, the large number of newly diagnosed patients may help resolve this problem. Diagnosis of large numbers of newborn infants with cystic fibrosis will permit controlled studies to determine the prophylactic value of the individual items of therapy that are controversial—particularly the use of face masks and tent aerosols, physical therapy, antibiotics, and dietary supplements.

Matching of patients by sex, birth weight, birth complications and family size, and also by random assignment to treatment groups will permit assessment of the value of these and other treatment variables for prevention of the first pulmonary complication. Such studies will eventually prove all aspects of treatment.[5]

Simultaneously with the proving of these items of therapy, there will have to be a broadened post-graduate training program for physicians in practice. This may include special post-graduate courses such as "Chronic Respiratory Diseases in Children and Adolescents," publication of the papers from such a course, formation of clinics satellite to a University Center, special fellowships for short-term study at a University Center, touring lectures, etc.

Conclusions

Prevention of the pulmonary complications of cystic fibrosis will become routine when (1) newborn diagnosis is routine, (2) the test techniques for prevention have been proven by controlled studies, and (3) knowledge of the application of these techniques is common to to all physicians who will have to care for these infants.

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Things You Cannot Waste

The courtesy you have shown a guest.
The attention you have shown your fellow man.
The flowers you sent a sick friend.
The effort invested in training a talent.
The strength spent in lifting another's burden.
The praise you gave a faithful employee.*

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*Culinary Almanac, 1949.

Genetic Counseling for Parents[*]

Children with Cystic Fibrosis, Agammaglobulinemia, or Fatal Granulomatous Disease of Childhood

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GENETIC COUNSELING involves the use of genetic information in order to promote the welfare of the individual, the family, and society. This becomes important for those types of chronic respiratory disease which have a clearly genetic etiology. When parents know that there is a sizable risk of producing another child with a serious defect, the responsible approach is to consider setting aside the privilege of further reproduction in order to protect the "rights" of children to be well-born.

The significance of such a choice was emphasized by the late Pope Pius XII: "Better warned of the problems posed by genetics and of the gravity of certain hereditary diseases, men of today have, more than in the past, the duty to take account of this increased knowledge so that they might forestall countless physical and moral difficulties for themselves and others. They should be attentive to whatever could cause lasting harm to their descendants and involve them in an interminable succession of miseries."[1]

If a couple is to make free and responsible decisions concerning future pregnancies, they should have: (a) the best information currently available about the genetic risks involved, (b) an interpretation of this information so that they can understand and accept it, and (c) techniques for restricting conception if they so decide. The parents may wish to consider other religious, emotional, or financial factors, but the final decision should be left to them.

The physician who makes the diagnosis of a genetic disease has the primary responsibility for seeing that the parents are informed of the genetic implications. The discussion is best conducted with both parents together, since both share in the need for understanding as a basis for future reproductive decisions.

The estimate of risk for the next pregnancy requires an accurate diagnosis and adequate information about the family history. A statement of "negative family history" is seldom sufficient. As a minimum, the record should answer the following questions: (1) Was the patient twin-born? (2) What was the outcome of each of the mother's other pregnancies? Were any children affected with a similar disease? (3) Are the mother and father related by blood? (4) How many brothers and sisters have the parents had? Has any had a problem similar to that of the patient?

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[*] Read at the Regional Continuation Course on Chronic Respiratory Diseases in Children and Adolescents at the University of Minnesota, Minneapolis, September 17, 1968.

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Mode of Inheritance

A decision as to the mode of inheritance is usually not difficult. All cases of cystic fibrosis follow an autosomal recessive inheritance, and all cases of fatal granulomatous disease of childhood appear to follow an X-linked recessive pattern. On the other hand, some cases of agammaglobulinemia are autosomal recessive, but others are of an X-linked recessive type. Parental consanguinity would strongly suggest an autosomal type, while the presence of affected maternal uncles would make X-linkage likely. If the laboratory data are equivocal, or if the family history appears to contradict the provisional diagnosis, further consultation would be advisable.

Two notes of caution may be helpful. With the relatively small current family size, isolated cases of genetic disease (having no family history of the condition) can be expected fairly often. The presence of disease in a girl does not always exclude X-linkage, since the occasional expression of an X-linked trait in carrier females has been observed.

Risks for the Next Pregnancy

In autosomal recessive traits (cystic fibrosis and some cases of agammaglobulinemia) the risk for the next pregnancy is 25 percent. The explanation of this risk to the parents may take some time, however.[2] They will need to understand that both husband and wife carry a "hidden" gene, and that the affected child by chance received a "double dose." There is no reason to blame themselves or each other for what has already happened, but they are now in a position to make a conscious choice about another pregnancy. The discussion may take into account their own adequacy in being able to care for another such child, as well as the severe health restriction that the child would face.

If contraception is attempted but fails, the 25-percent risk of severe defect in the child could be considered a fetal indication for abortion. Rather than run any risk at all, the couple may prefer voluntary sterilization for husband or wife.

In X-linked recessive situations (fatal granulomatous disease and some cases of agammaglobulinemia) the risk for the next pregnancy is 25 percent *or less*. The possibility of a lower risk arises from the fact that one third of the *isolated* cases of an X-linked *lethal* trait will result from a newly mutant gene on the X-chromosome from a non-carrier mother. In these newly mutant cases the risk for the next pregnancy is essentially zero. For example, if the mother of an affected boy has two normal brothers and two normal sons and no other affected relatives, there is only a 24-percent chance that she is a carrier and thus a 6-percent chance that the next child will be affected (Table 1). If there had been one additional affected brother or son, we would know that she *is* a carrier and that the risk for the next pregnancy would be 25 percent. If a woman is demonstrated to be a carrier, neither sterilization of her husband nor donor insemination

TABLE 1

Probability That the Mother of an Isolated Case is a Carrier for an X-Linked Lethal Recessive Trait

Number of unaffected brothers (with none affected)	Number of unaffected sons (with only one affected)				
	None	One	Two	Three	Four
None	0.67	0.50	0.33	0.20	0.11
One	0.60	0.43	0.27	0.16	0.09
Two	0.56	0.38	0.24	0.14	0.07
Three	0.53	0.36	0.22	0.12	0.07

Adapted from Murphy[3]

TABLE 2

Probability That a Woman is a Carrier for an X-Linked Recessive Trait

Steps from known carrier	Number of unaffected sons (with none affected)				
	No sons	One	Two	Three	Four
One	0.50	0.33	0.20	0.11	0.06
Two	0.25	0.14	0.08	0.04	0.02
Three	0.13	0.07	0.03	0.02	0.01
Four	0.06	0.03	0.02	0.01	0.004

Adapted from Murphy[3]

would be indicated.

Other Relatives

The risk to other relatives should also be considered. In the case of cystic fibrosis, each sibling of a parent (of affected children) has a 50-percent chance of being a carrier, and their spouses have about a 4-percent chance. The over-all risk for a cousin of an affected child is about 1/200.

If a cystic fibrosis patient marries, all children will be carriers of a gene for the trait. In such a marriage the spouse should always be tested for carrier status to reduce the chances of producing an affected child. This problem is less critical for males with cystic fibrosis, since most are sterile.[4]

The need to check other relatives is greater for X-linked recessive traits. If a sister of a known carrier (or of an affected male) has two normal sons (and none affected), there is a 20-percent chance that she is a carrier and thus a 5-percent chance that her next child will be affected (Table 2). If she has one or more affected sons, she is known to be a carrier.

Concluding Comments

Tests for carrier detection are not yet accurate and simple enough for premarital counseling in the general population. Even for a condition as common as cystic fibrosis, at least 800 persons would have to be tested in order to detect one couple in which both are carriers. However, carrier tests are most helpful for close relatives of affected persons.

The services of a geneticist as consultant may be helpful in interpreting a family history, in tracing family members, or in other ways. Within Minnesota such consultation can be obtained from the Human Genetics Unit of the Minnesota Department of Health. A directory of genetic services in other states has been published recently.[5]

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From an 18th Century French Drug Dictionary

"All parts of man, his excrescences and excrements, contain oil and sal volatile, combined with phlegm and earth. Skull, brain, and calculus are employed in medicine, and are referred to in their proper places. Burning hair, smelt by patients, will counteract the vapors. Moss of the human skull, human blood, and human urine all have their uses in medicine. The saliva of a robust young man, taken fasting, is an antidote against the bites of serpents and mad dogs. Wax from the ears is good against whitlows. Nails from the fingers and toes, given internally either in substance or infused in wine, make a good emetic. Women's milk is pectoral, good in phthisis, and useful to apply to inflamed eyes. Fresh urine, two or three glasses drunk in the morning fasting, is good against gout, hysterical vapors, and obstructions. It may also be applied externally in gout and in skin complaints. Excrement of man can be applied to anthrax, plague bubos, and quinsies. Dried and powdered, it is recommended in epilepsy and intermittent fevers. Dose, one scruple to a drachm."*

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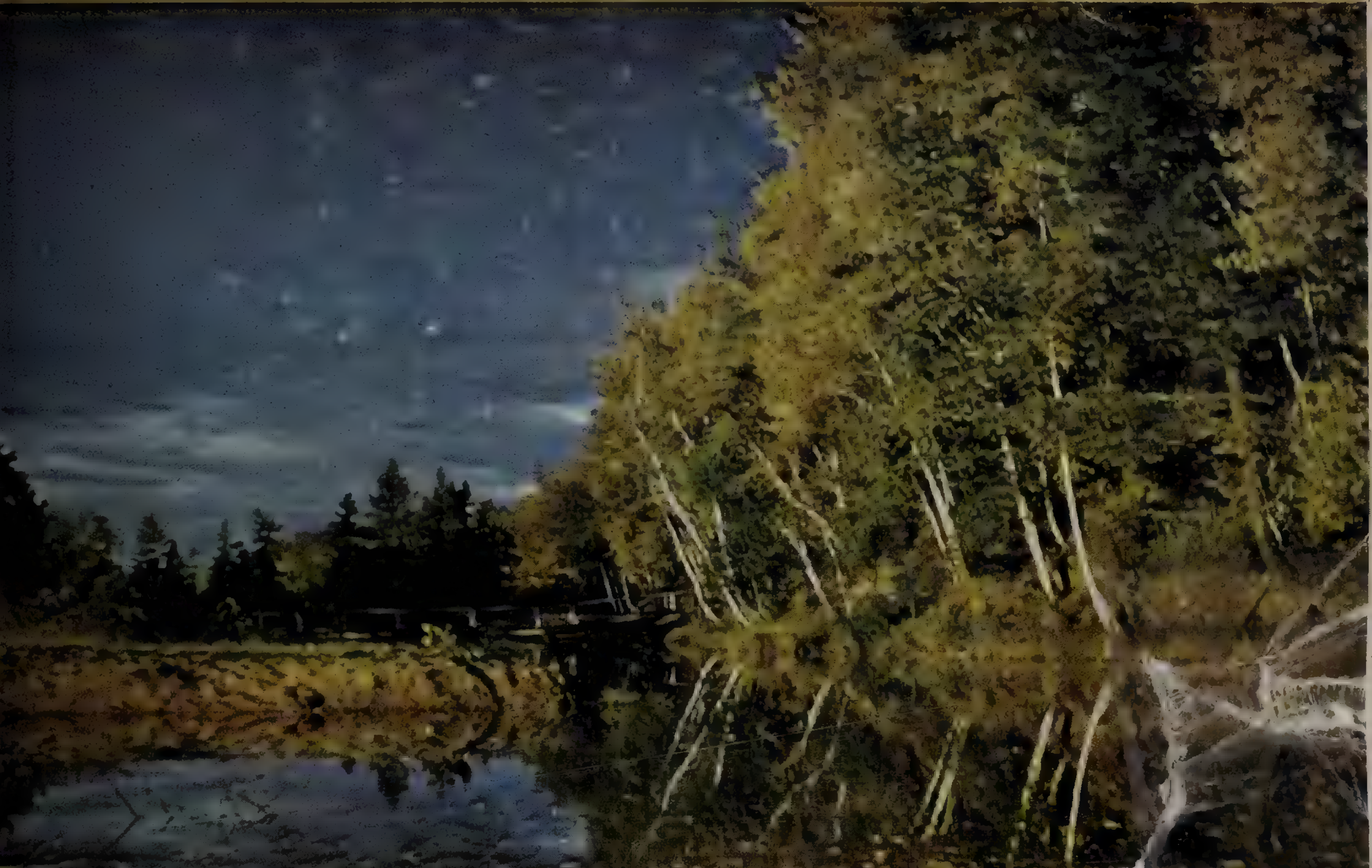

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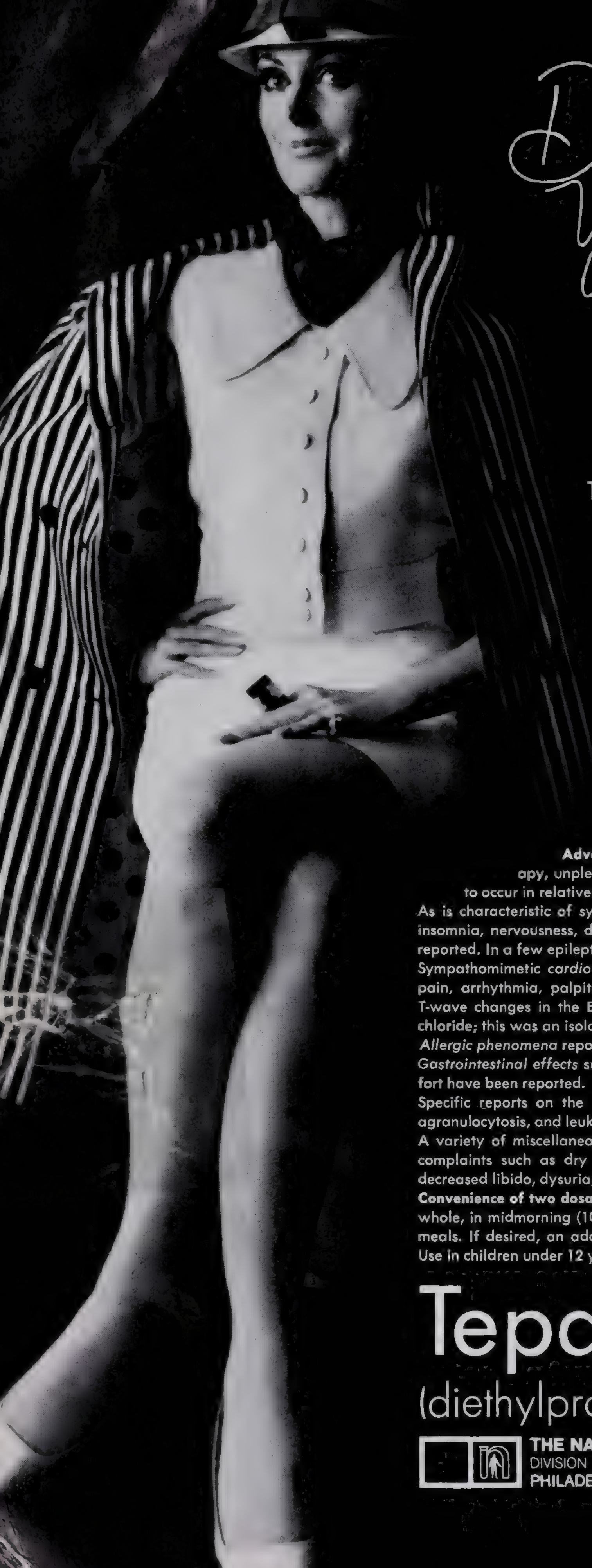

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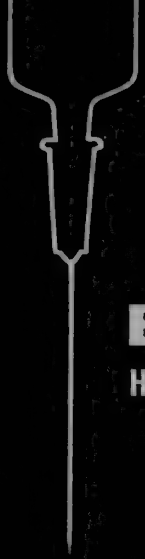

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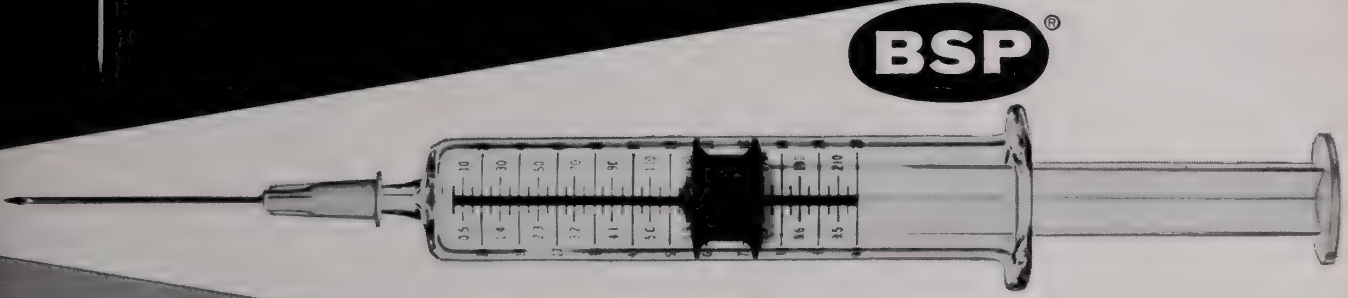

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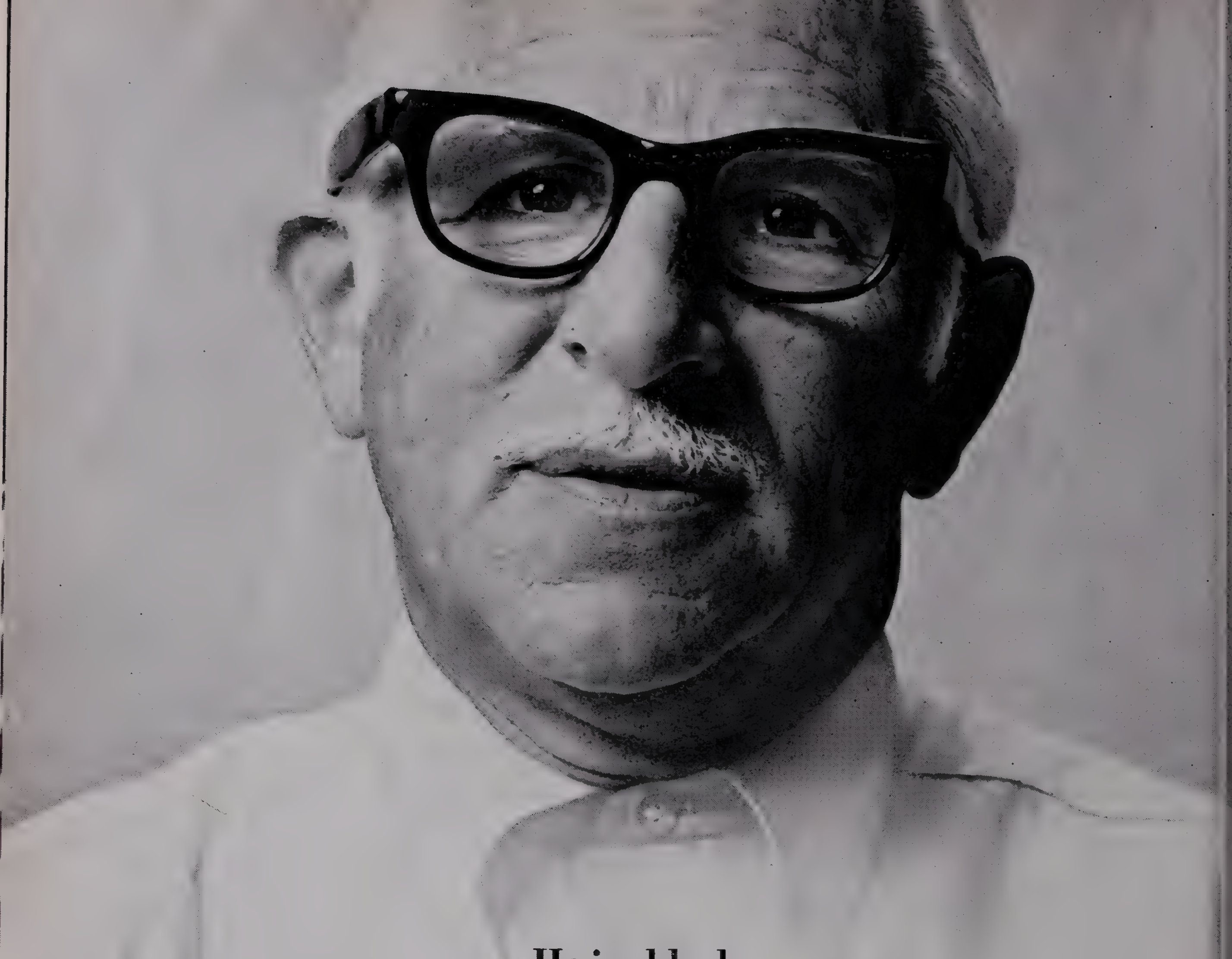

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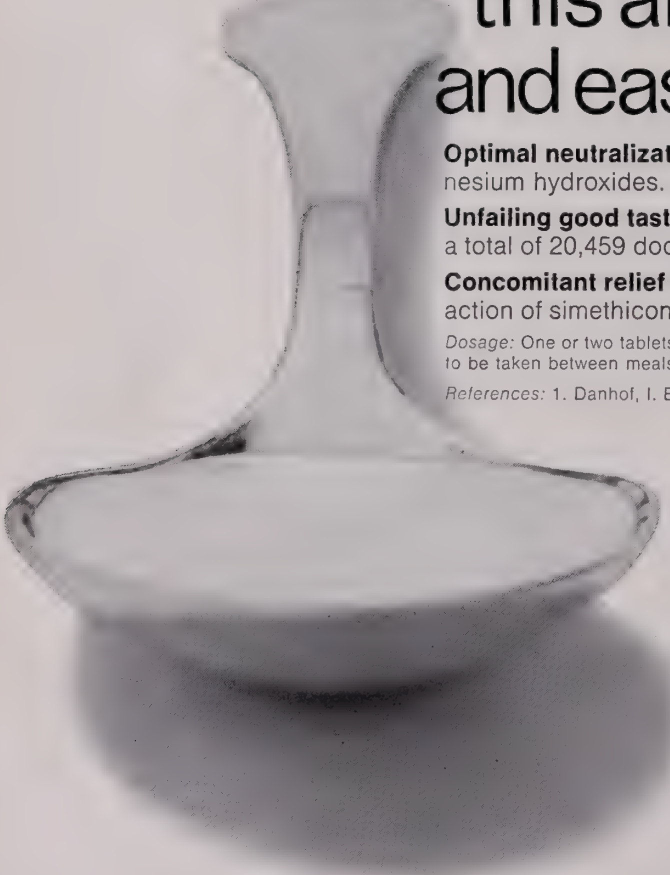

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President's Letter

Dermatology in Minnesota

THE ECONOMIC loss from cutaneous medical problems recently was estimated conservatively as representing 1.43 billion dollars per year.[1] This figure includes the cost of medication, hospitalization, losses in wages, and funds for compensation. No estimate of Minnesota's share of this loss is available, but our climate, the size of our population and the nature of the industry of the state indicate that probably our share is lower than that of many other states.

We are well provided with specialists in dermatology. There are 68 dermatologists in Minnesota, or one per 52,000 of the general population. Minnesota ranks thirteenth in the number of dermatologists within its borders. Missouri, with one million more population, has only three more dermatologists. The ranking of Minnesota in terms of dermatologists-to-population is even better, for it is seventh, ahead of New Jersey, Michigan, Ohio, Pennsylvania, Texas, Illinois and Wisconsin. This indicates that we not only train dermatologists in our state, but also retain them and attract others to practice here.

Nationally, dermatology ranks after internal medicine and pediatrics in terms of numbers of persons in full-time medical specialty practice. In 1966 there were 3,674, of whom 2,111 were board-certified. By comparison, one must note that at the same time only 884 of 2,047 cardiovascular specialists were board-certified and only 8,551 of 16,417 pediatricians were board-certified.

Minnesota has been regarded as a center of excellence in training in dermatology. Beginning with the internationally recognized program developed under Dr. Henry E. Michelson at the University of Minnesota and continuing with the sophisticated basic sciences and clinical sciences approach under the direction of Dr. Francis Lynch, the Department of Dermatology at the University of Minnesota has maintained its position as a leader among such facilities in the Big Ten universities. Minnesota and Michigan are acknowledged to be the prime schools of dermatology training. The Section of Dermatology at the Mayo Clinic has a postgraduate training program which was brought to national prominence by Dr. Paul A. O'Leary and has continued to advance under the guidance of Dr. Louis A. Brunsting and Dr. Robert R. Kierland. Minnesota trains between 5 and 7% of the nation's dermatologists, or, stated differently, has 32 men in training at any one time. Between 1963 and 1968 the number of training programs in dermatology declined by 30%; but at the same time, the number of approved residencies increased to 530.

Thirty-two training programs in dermatology, made possible by grants from the National Institutes of Health, are currently in operation. These programs have been developed to train dermatologists to meet the requirements for a full-time career in the basic and clinical sciences related to dermatology. Two of the centers made possible by these grants are in Minnesota, at the University of Minnesota and at the Mayo Clinic. Both institutions have trained a large number of the heads of departments of dermatology in medical schools in this country,

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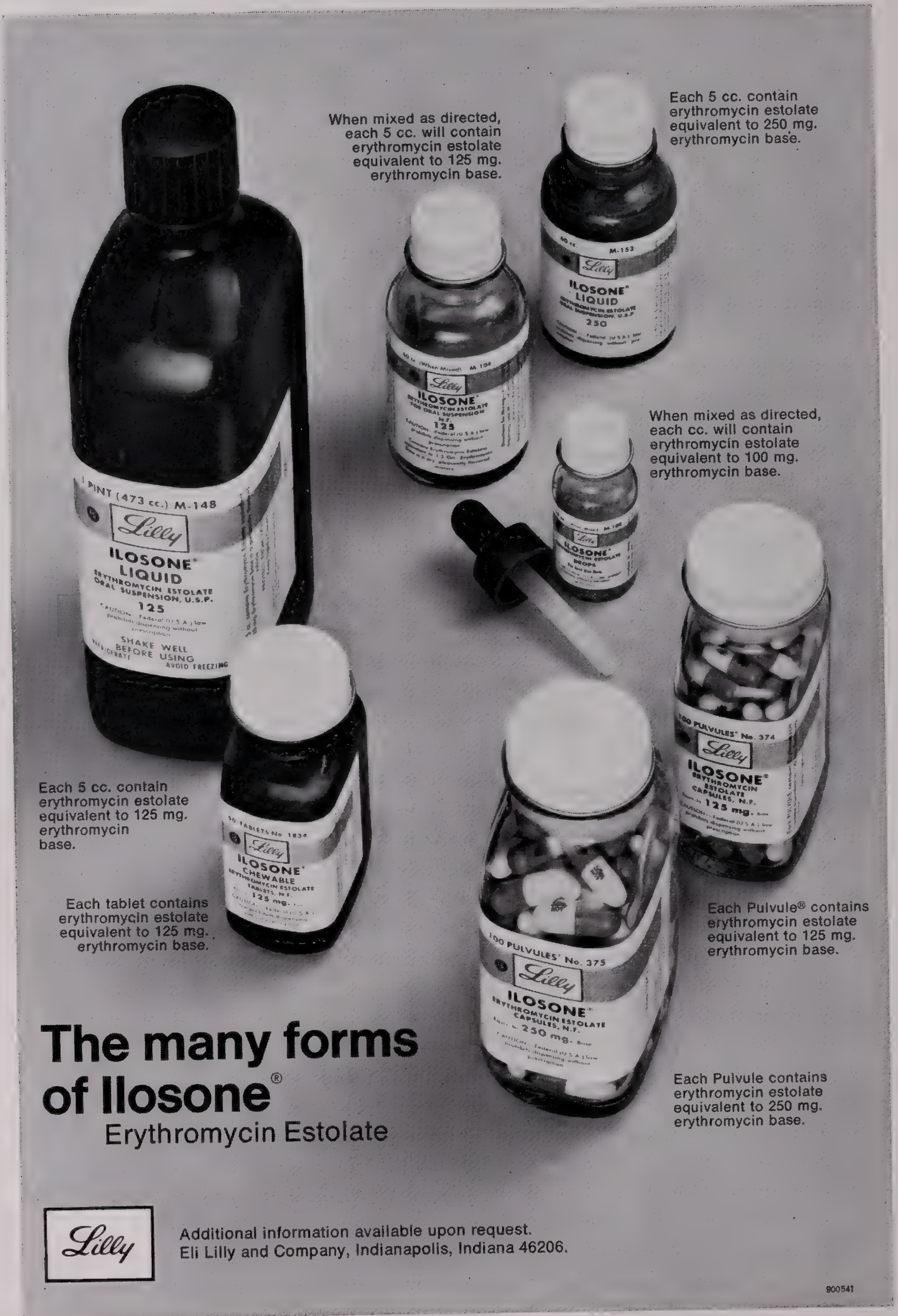
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Treatment of Coronary Disease*

Pathologic Limitations

JESSE E. EDWARDS, M.D.
St. Paul, Minnesota

WHEN MAN MAY COME closer to the moon than the distance between St. Paul and Rochester, when one man may live with the heart of another, the word limitation must allow for changing parameters.

In recent years progress in medicine has been so great that, in discussing anatomic limitations to therapy in coronary disease, one must recognize certain conditions. Thus, limitation with regard to medical treatment without the facilities of an acute cardiac care unit differs from that with such a unit. Under certain circumstances limitation may be nearly absolute from the viewpoint of medical treatment, while surgical treatment may offer predictable beneficial results. In any case, that which is limited today may be commonplace tomorrow. It is apparent that our discussion today of pathologic limitations to the treatment of coronary arterial disease must reflect that what is pertinent today is subject to change within the future, in some instances within the near or very near future.

Coronary Atherosclerosis

The clinical opinion that coronary atherosclerosis is present, either from a history of angina pectoris, from myocardial infarct having occurred, or from both, is commonplace, and much thought has been given to means of altering this fundamental arterial lesion. One aim has been through application, in reverse, of those two factors which have been identified as having an atherogenetic tendency: elevated serum lipids and hypertension. The high content of collagen and extracellular lipids in the intimal lesion appears to fix the lesion securely—so securely, in fact, as to be resistant to significant alteration by any manipulation of diet and blood pressure (Figure 1a).

In addition, an occasional arterial segment is the site of a thrombus in the organized stage (Figure 1b). This process is characterized by

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the presence in the lumen of connective tissue with varying degrees of vascularization. The connective tissue here, as in the fundamental atheroma, is essentially scar tissue, a substance highly resistant to change.

It is evident that if dietary and other manipulations are to affect atherosclerosis, these must be applied before the lesion develops. In practical terms this means that measures aimed at preventing atherosclerosis must start at and be continued from early ages, from adolescence or even from childhood.

Recognizing that the established lesion is not readily changed by manipulation of atherogenic factors, attention has been directed toward surgical alteration of lesions, alterations which might include removal of atheromas or removal of segments (with grafting) of diseased coronary arteries. Swedlund and associates[1] attempted to determine how practical was the potential for such surgical procedures. They studied specimens of hearts from patients who had had clinical evidence of coronary disease and observed that in only a limited percentage of the cases (18 percent) was the lesion localized to one focus, while in the remainder, multiple lesions were encountered. This is a relatively small percentage of patients who might receive considerable benefit from surgical treatment of the fundamental lesion.

Acute Myocardial Infarction

A number of problems relate to acute myocardial infarction which represent relative or absolute limitations to treatment by today's standards:

Shock

Shock occurring with acute myocardial infarction may be a manifestation of loss of muscle, either from the acute event alone (Figure 2a) or added to loss from earlier episodes of infarction (Figure 2b) to the degree that there is an absolute and irreparable loss of efficiency of the pumping function of the left ventricle. It is important to emphasize, however, that shock may be a manifestation of factors other than myocardial and that, when these are overcome, it becomes evident that the left ventricle has sufficient reserve to perform in an efficient manner.

Cardiac Rupture

Rupture of the heart (including rupture of the free wall of the left ventricle, of the ventricular septum, or of a papillary muscle) is not uncommon among cases of fatal acute myocardial infarction, occurring in about 15 percent of such cases. If one were to accept that 15 percent of patients with acute myocardial infarction fail to survive, one might estimate that among one hundred instances of acute

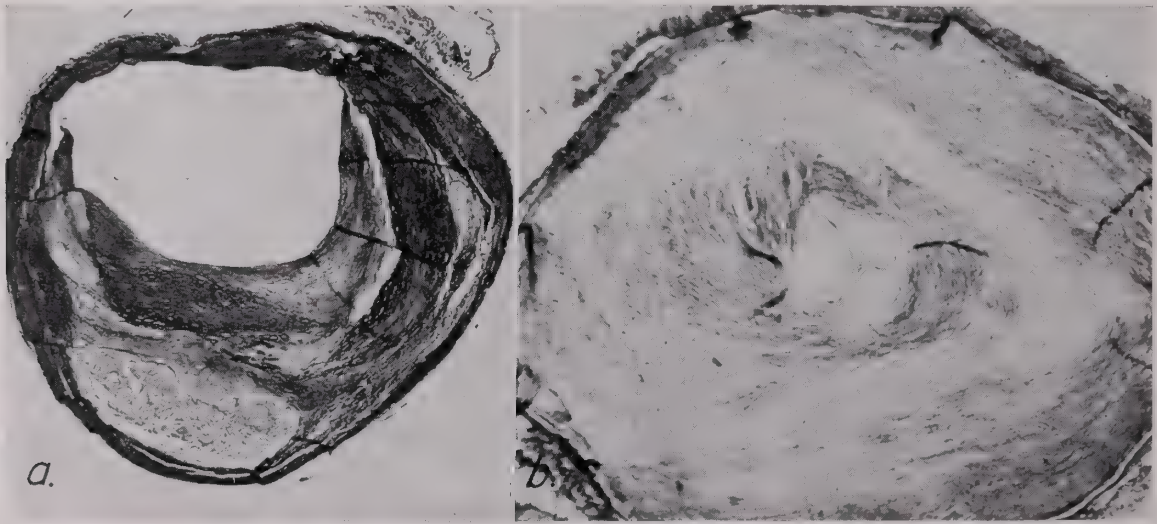

Fig. 1—Photomicrographs of atherosclerotic coronary arteries. *a.* The basic atheroma is composed of collagen and extracellular connective tissue. Elastic tissue stain; x 18. *b.* In addition to an atheroma which is highly collagenous, the narrowed lumen contains an organized thrombus represented by vascular connective tissue. Elastic tissue stain; x 15.

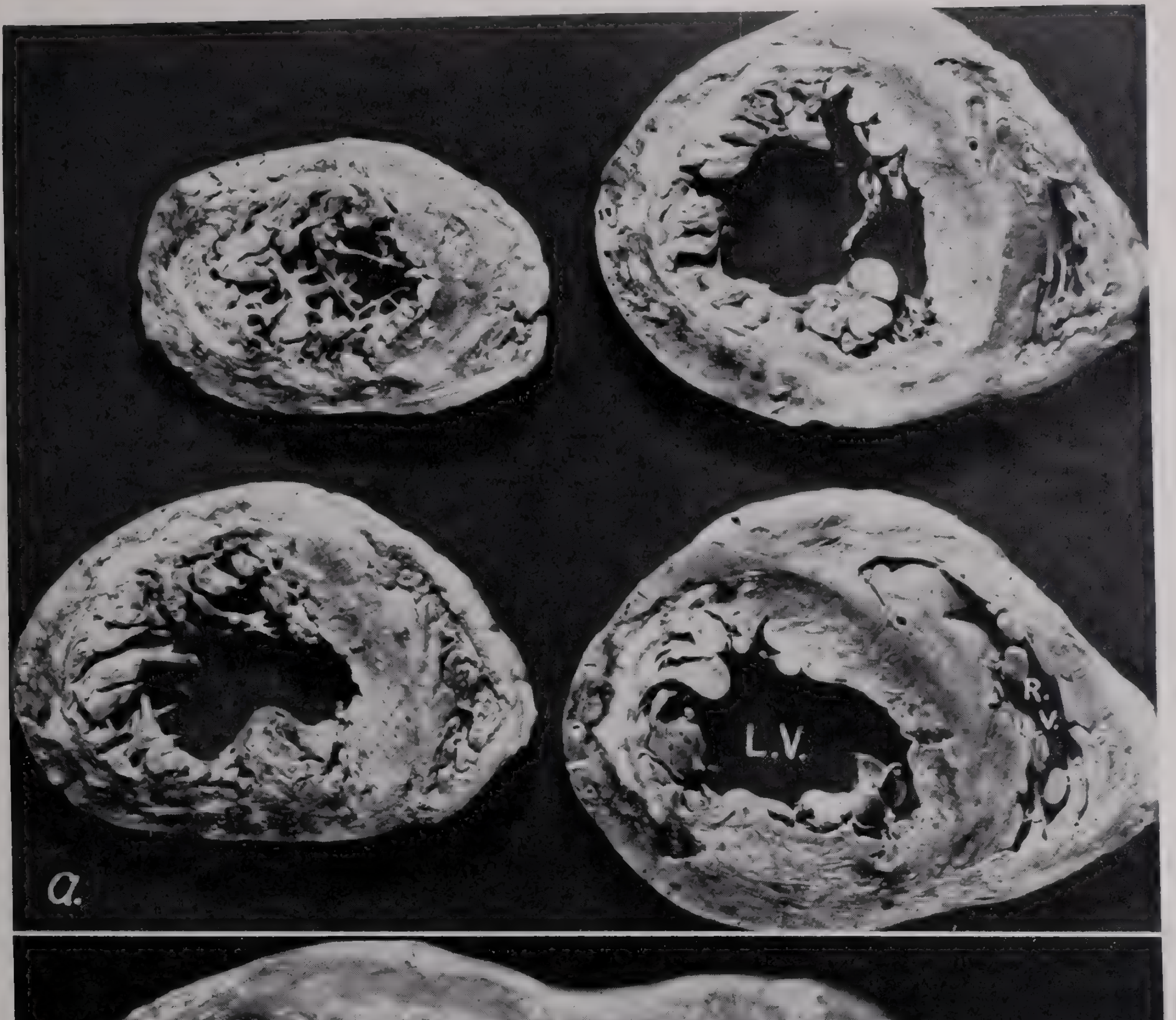

Fig. 2—Extensive myocardial infarction. *a*. The anterior, lateral and posterior walls of the left ventricle are involved by extensive acute infarction. *b*. In addition to a healed subendocardial anterior infarct, the posterior wall shows extensive acute transmural myocardial infarction. In these illustrations, as well as in others, L. V. = left ventricle; R. V. = right ventricle.

myocardial infarction, there occur about two cases of rupture of the heart. In most instances, this complication represents a major barrier to effective therapy of the patient since death usually (but not always) follows shortly after the episode of rupture. (See below for consideration of left ventricular aneurysm developing from rupture of the heart.)

All instances of rupture of the heart occur in transmural myocardial infarction and most commonly about three to four days after the onset of the acute infarction.

About 85 percent of the cases of rupture involve the free wall of the left ventricle. The complication begins as a laceration of the left ventricular wall at the junction of infarcted and non-infarcted muscle. Blood from the cavity extends from the laceration through the left ventricular wall and into the pericardial sac (Figures 3 and 4). Classically, acute cardiac tamponade and death from the resulting hemopericardium occur within minutes after the extravasation of blood into the pericardial cavity.

Rupture of the ventricular septum, more commonly a complication of posterior than of anterior myocardial infarction, occurs in about ten percent of all cases of cardiac rupture (Figure 5). The resulting acquired ventricular septal defect varies in its manifestations. In those instances where the opening is wide, the circulation rapidly fails. Less commonly, the circumstances are such as to allow the patient to live for varying periods of time, even years after the event of rupture. Such patients are candidates for surgical closure of the acquired defect.

The least common type of rupture of the heart is characterized by loss in continuity of a papillary muscle (Figure 6). This complication, which represents about five percent of all instances of rupture of the heart, usually involves the posteromedial papillary muscle in

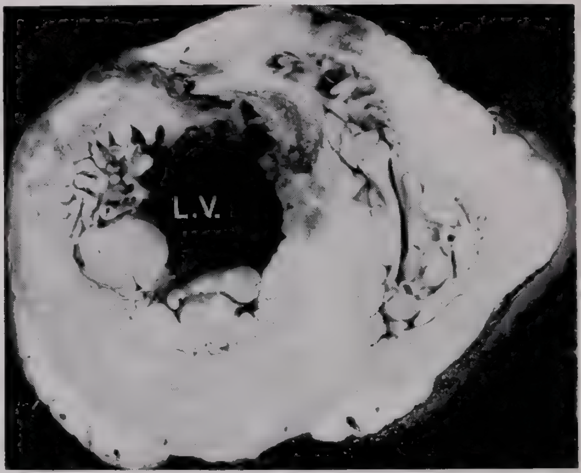

Fig. 3—Transmural myocardial infarction of anteroseptal region of left ventricle with laceration of left ventricular wall characteristic of rupture of the heart.

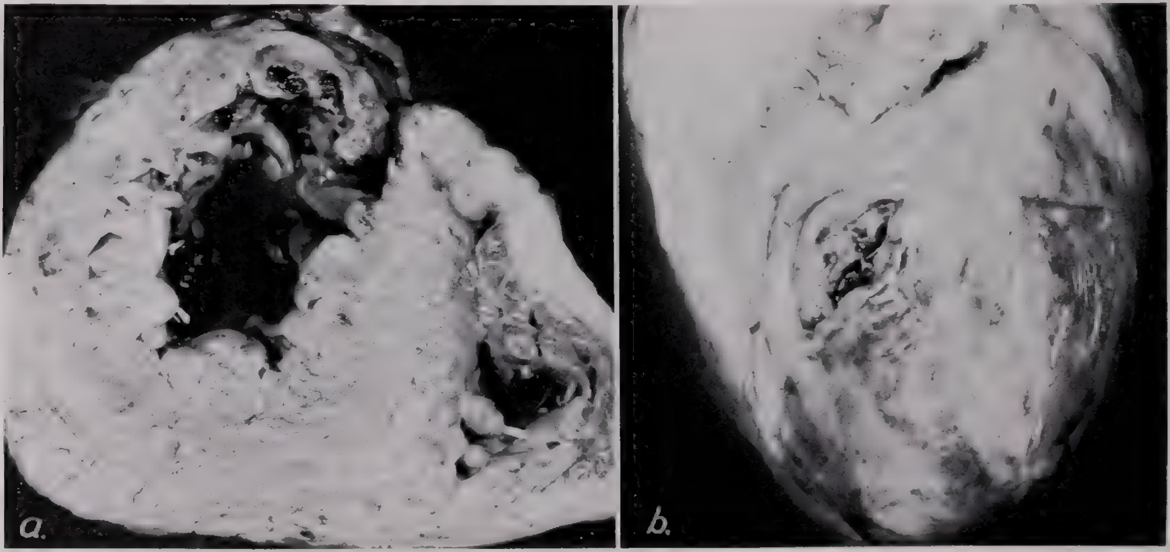

Fig. 4—Rupture of the anterior wall of the left ventricle characterized by an opening larger than average. *a.* Cross section of the ventricular portion of the heart. The rupture site lies at the periphery of the myocardial infarct which is at the junction of the anterior wall and ventricular septum. *b.* External view of the anterior wall of the heart showing a gaping wound which led to hemopericardium. In most instances, the epicardial aspect of the rupture is less distorted than in this instance.

continuity with infarction of the posterior left ventricular wall. The resulting mitral insufficiency is usually of major proportion and responsible for early significant failure of the circulation and death.

While the onset of major mitral insufficiency in patients with acute myocardial infarction is often the result of rupture of the papillary muscle, there are exceptions (Figure 7). Extensive infarction of a papillary muscle without rupture may, on occasion, be responsible for significant incompetence of the mitral valve. Before leaving the subject of rupture of the heart, reference should be made to *hemopericardium complicating acute myocardial infarction in the absence of cardiac rupture.* Such relatively uncommon situations represent bleeding into the pericardium from an organizing pericarditis. Fibrinous pericarditis in myocardial infarction is, for practical purposes, a complication of transmural infarction.[2] When present, the pericarditis is always found over the infarct; but in some cases it may involve the pericardium diffusely. In such cases, in particular, significant hemorrhage may occur during that stage of the pericarditis when a layer of granulation tissue has developed as part of the process of organization of the inflammatory process. While a program of anticoagulation has a positive influence in causing bleeding from pericarditis, hemorrhage of significant proportion may occur even when no anticoagulants have been administered.

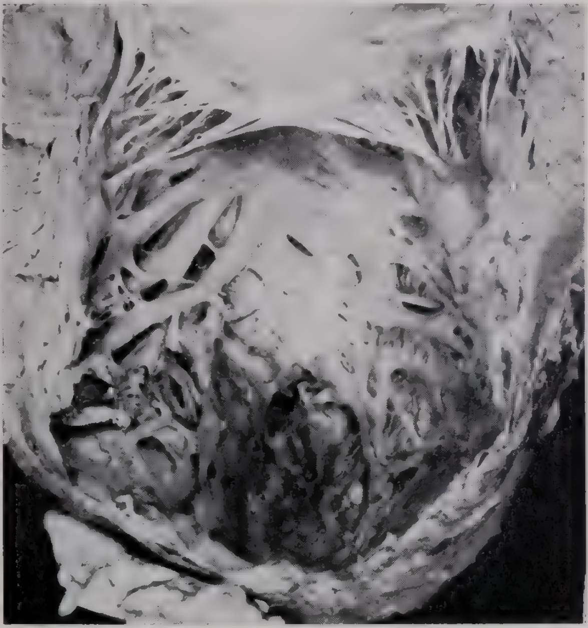

Fig. 5—Rupture of ventricular septum. Interior of left ventricle. The point of the arrow lies at the site of a rupture of the ventricular septum. In this instance there is extensive infarction, the rupture occurring at the junction between the infarcted and non-infarcted portions of the septal wall.

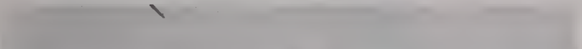

Fig. 6—Rupture of the posteromedial papillary muscle of the left ventricle. The ragged edges (between arrows) of the ruptured papillary muscle are evident. The upper remnant of the papillary muscle along with the chordae is looped through an interchordal space.

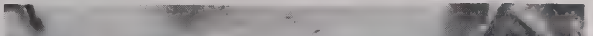

Fig. 7—Extensive infarction of the left ventricular wall represented by the lighter zone in the muscle and associated with infarction of the postero-medial papillary muscle (P.-M.). The latter, discolored in the fresh specimen, shows atrophy in this photograph.

Cardiac Irregularity

Arrhythmias, although occurring commonly during episodes of acute myocardial infarction, usually leave no specific signs that can be recognized anatomically. Only uncommonly does the pathologist find infarction of the major conduction tissue (as part of a posterior-basal myocardial infarct) from which he might infer that atrioventricular dissociation has occurred. From clinical experience ventricular fibrillation is recognized as a common basis for the sudden death that may occur in patients convalescing from acute myocardial infarction. In such cases pathologic study supplies evidence in a negative way that is consistent with such a serious arrhythmia.

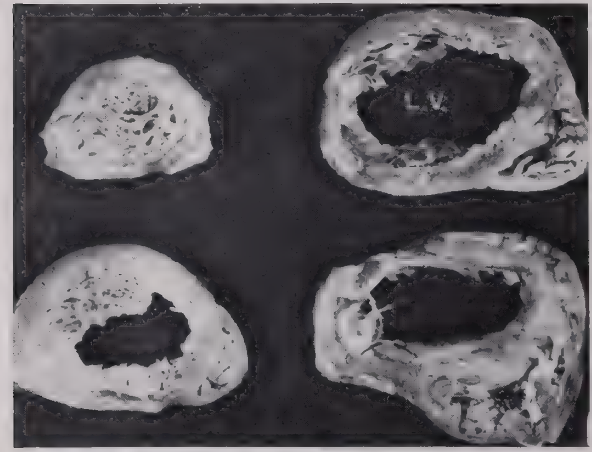

Fig. 8—Cross sections of the ventricular portions of the heart in a case with extensive healed myocardial infarction leading to congestive cardiac failure.

The negative evidence takes the following form. The clinically recognized infarct is found but no additional lesions are identified which would explain the sudden catastrophe. Search at the periphery of acute myocardial infarcts shows viable muscle intermingled with infarcted muscle. As infarction is present in the general area, one concludes that ischemia had been present and that it had been shared by the muscle which survived. Such accumulations of living muscle are probably potentially dangerous foci for spontaneous generation of uncoordinated impulses.

Thromboembolism

Thromboembolism continues to represent an element to recovery in acute myocardial infarction; nevertheless, pulmonary embolism appears to be less common today than two

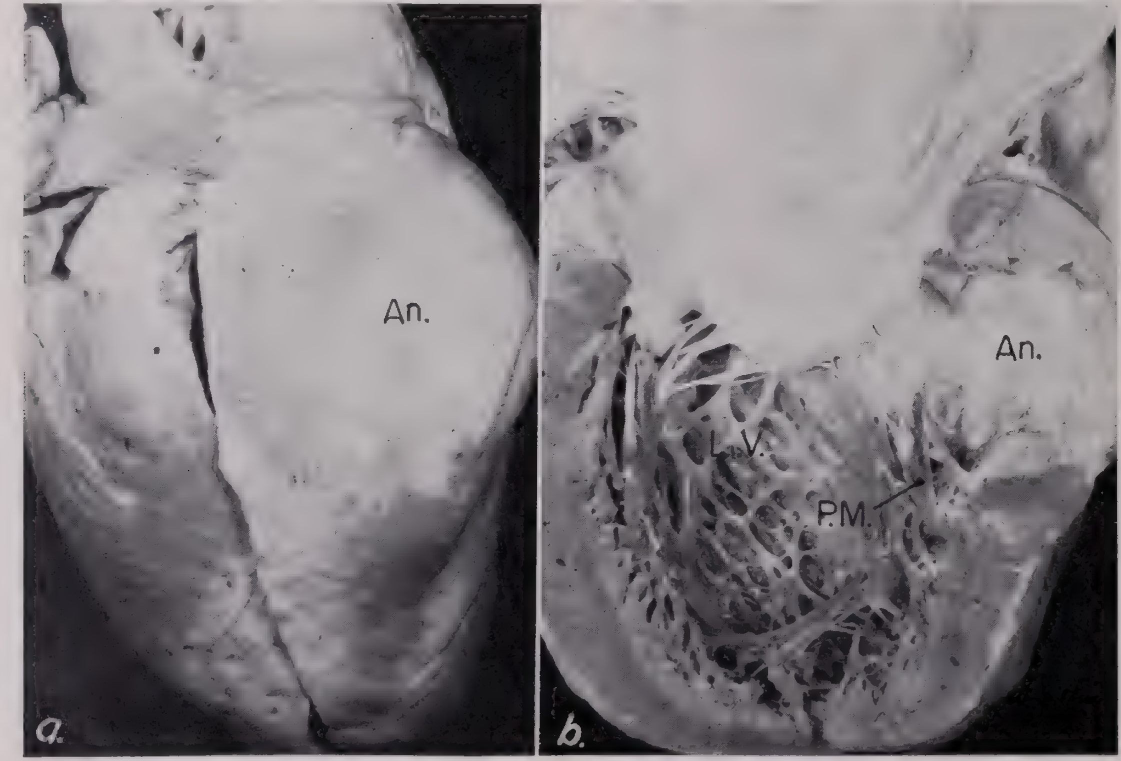

Fig. 9—Aneurysm (An.) of posterior wall of left ventricle. *a.* External view of heart viewed from left. *b.* Section through the aneurysm and adjacent portion of the left ventricle. In this position, the aneurysm lies closely aligned with the posteromedial papillary muscle (P.M.).

decades ago. This may reflect the fact that in the treatment of acute myocardial infarction administration of anticoagulants and early ambulation are common practices.

In some cases with infarction of extracardiac organs, the evidence strongly favors embolism from a complicating left ventricular thrombus. In other cases, the evidence for embolism is not clear, infarction of an extracardiac organ possibly resulting from a combination of lowered blood pressure and arterial disease located in the organ infarcted. In general, the following rule holds true, namely, that systemic arterial thromboembolic complications usually attend large (transmural) infarcts when there is myocardial failure rather than with those of subendocardial distribution.

Healed Myocardial Infarction

The state of patients carrying healed myocardial infarcts is so broad as to vary from no evidence of disease to irreparable cardiac failure.

For those patients with evident disability, the clinical state takes three main patterns:

Cardiac Failure from Muscle Loss

Congestive cardiac failure from extensive loss of muscle, other than that associated with a left ventricular aneurysm, is usually the result of several episodes of myocardial infarction, although the factor of multiplicity of lesions may not have been apparent clinically (Figure 8). In some patients each of the several areas of infarction is healed, the problem being one of chronic inadequacy of the myocardium. In other patients, the state of cardiac efficiency may have been maintained until an additional acute myocardial infarct makes its appearance. With this event, irreversible failure of the pumping function of the heart may become established as a consequence of the additional loss of muscle incident to the new infarct.

Aneurysm

Left ventricular aneurysm is usually the result of myocardial infarction; in such circumstances the underlying lesion is of the transmural type.

Classically, some myocardial tissue remains in the zone of the infarct, and the thinned wall gradually bulges to form a true aneurysm (Figures 9 to 11). Less commonly, left ventricular aneurysms complicating myocardial infarction are of the false type (Figure 12), which result from rupture of the free wall, but without resulting hemopericardium. In such cases, adherent pericardium tends to restrain the extent of the hematoma; the latter, in turn, organizes to form a fibrous wall of a cavity that communicates (usually through a narrow opening) with the left ventricular cavity. In general, the behavior of left ventricular aneurysms is the same, whether of the true or false type.[3]

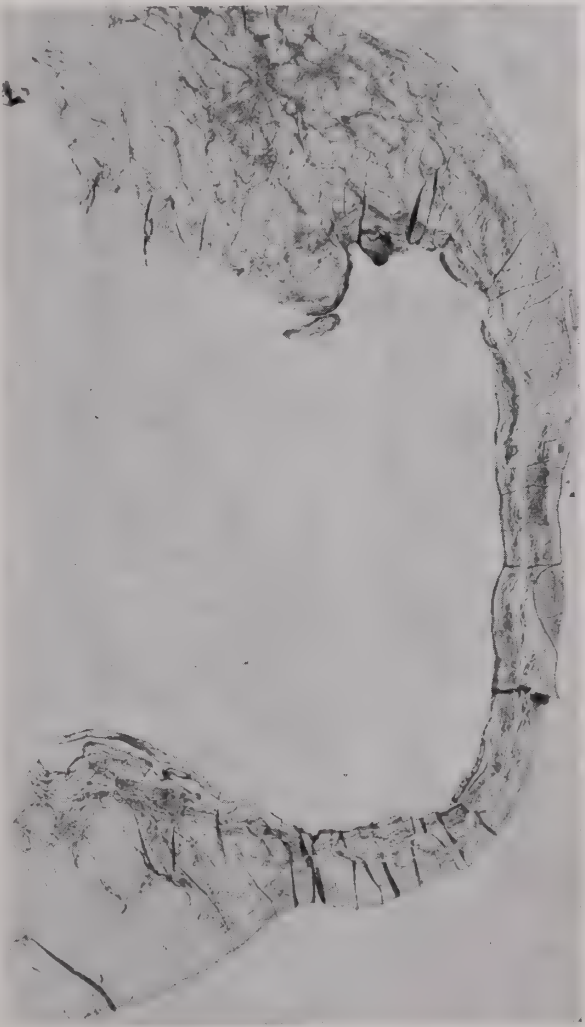

Fig. 10—Low power photomicrograph of left ventricular aneurysm shown in Figure 9. This aneurysm is of the true variety; remnants of myocardium appear in the aneurysm wall. Elastic tissue stain; x 6.

Some patients with left ventricular aneurysm may exhibit no apparent disability; but, in general, the patient with a left ventricular aneurysm tends to exhibit some loss of left ventricular efficiency, at times to the point of overt congestive cardiac failure. The basic problem is that, during ventricular systole, the wall of the aneurysm bulges outward, while the rest of the muscle contracts. The waste of energy involved in the paradoxical motion of the aneurysm may be the important factor underlying left ventricular failure. Additional factors are involvement of a papillary muscle by the underlying infarct (with a tendency toward mitral insufficiency) and the general factor of loss of a large area of infarction which underlay the formation of the aneurysm.

At present, when resection of a left ventricular aneurysm is possible, certain limitations should be emphasized. In the majority of cases, the underlying infarct is anterior in position, with some, but usually limited, involvement of the anterior papillary muscle.

Less commonly, the underlying infarct lies in a posterior position and may concomitantly involve the posteromedial papillary muscle extensively. From the point of view of damaging a papillary muscle by resection of a left ventricular aneurysm, those aneurysms lying anteriorly seem to be less vulnerable than those lying posteriorly.

Regarding indications for resection, the major one is congestive failure, a lesser one is recurrent systemic embolism from the thrombus that almost invariably lies in the cavity of the aneurysm.

Rupture of a ventricular aneurysm is an uncommon event and at present is less likely to occur than are serious complications of aneurysmal resection.

When a surgical procedure in any part of the heart leaves a blind recess of a cavity, a thrombus is apt to form. This has been demonstrated repeatedly in cases of "closed" mitral commissurotomy when the left atrial appendage is incompletely resected. Similarly, a recess left after resection of a left ventricular aneurysm invites the formation of a mural thrombus and the chances of complicating systemic embolism (Figure 13).

Mitral Insufficiency

Mitral insufficiency occurring as part of a healed myocardial infarction probably has a complex basis in most cases.

In those patients with extensive loss of muscle and congestive cardiac failure, several factors appear to contribute to this valvular dysfunction. Among these is dilatation of the left ventricular chamber with (a) secondary enlargement of the mitral orifice and (b) altered orientation of the papillary muscles. Frequently the papillary muscles are sites of infarction along with the free wall (Figure 14). Involvement of these structures is probably a contributing factor in mitral insufficiency.

In some situations (and not uncommonly) one finds a healed posterior subendocardial scar of myocardial infarction along with a scarred posteromedial papillary muscle. In such cases the left atrium is often found enlarged, but a positive correlation with clinical evidence of mitral insufficiency does not consistently occur.

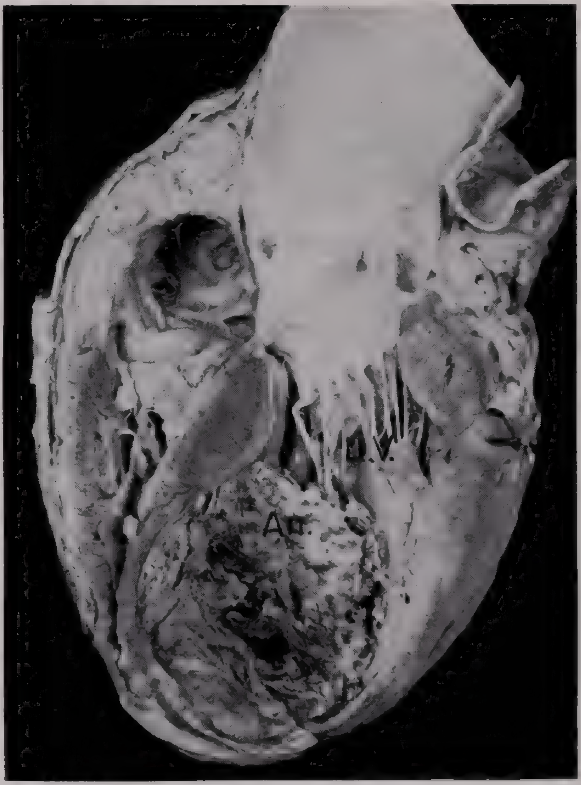

Fig. 11—Aneurysm of left ventricle resulting from infarction of anteroseptal region of left ventricle. Characteristically, the aneurysm contains a mural thrombus.

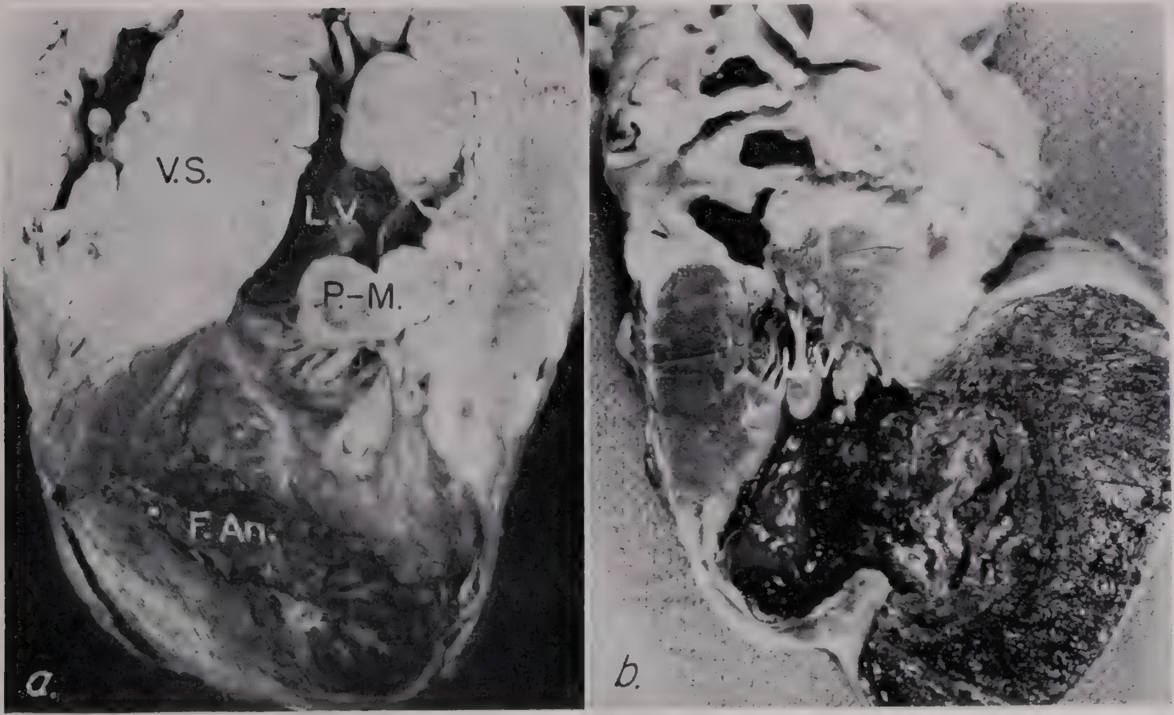

Fig. 12—Two examples of false aneurysm (F. An.) of the left ventricle resulting from rupture of heart. *a.* The heart is sectioned in a tangential way, showing the false aneurysm at the junction of the ventricular septum (V. S.) and the posterior wall of the left ventricle. P.-M. = posteromedial papillary muscle. *b.* Sagittal section through the left ventricle showing a characteristic false aneurysm in which the neck of the aneurysm is considerably more narrow than the fundus.

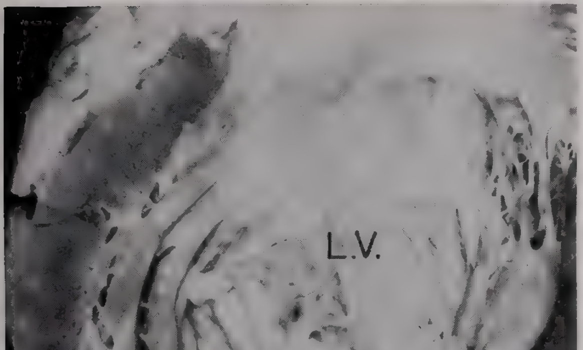

Fig. 13—Interior of left ventricle showing site of previous resection of a left ventricular aneurysm. At the recess, resulting from the excision and suture at the site of resection of the aneurysm, there is a thrombus (between arrows) which represents a potential source for embolism.

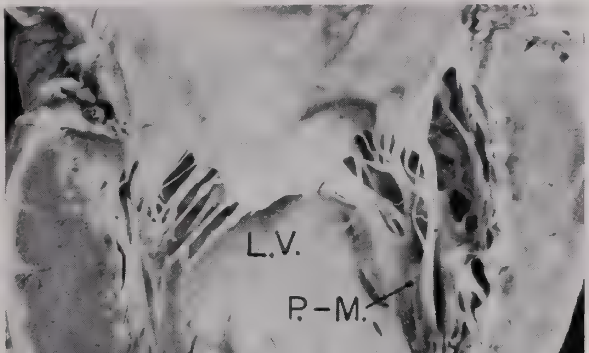

Fig. 14—Interior of left atrium and ventricle in an instance of subendocardial posterior myocardial infarction with concomitant involvement of the posteromedial papillary muscle (P.-M.). The latter is markedly atrophic. Such a lesion may underlie mitral insufficiency.

Conditions Associated with Coronary Disease

A distinct limitation to the treatment of coronary disease is that other diseases may be associated.

Hypertension and Calcific Aortic Stenosis

In the presence of hypertension or calcific aortic stenosis, associated with acute myocardial infarction, the tendency for development of congestive cardiac failure is greater when myocardial infarction occurs than in those instances wherein myocardial infarction is not associated with a condition causing myocardial strain.

Diabetes

Diabetes not only exerts an effect favorable to atherosclerosis and myocardial infarction but, in the event of acute myocardial infarction, may tend to upset the balance of diabetic control.

Myxedema

A trying factor is myxedema. This condition favors the development of atherosclerosis. The increased metabolic rate resulting from treatment of myxedema tends to favor the development of myocardial ischemia.

Cerebral Vascular Disease

Cerebral vascular disease with ischemic loss of cerebral tissue may represent a serious complication of myocardial infarction. In other instances, this condition is coincidentally present as a factor which tends to complicate the management of the total case.

Among patients with aortic atherosclerosis of degrees sufficient to cause either an aortic aneurysm or thrombotic occlusion of the abdominal aorta, coronary atherosclerosis is commonly present, a factor which represents a potential for serious acute complications among those patients who manifest protracted hypotension incident to bleeding from the aneurysm. Also, underlying coronary disease and its complications represent the basis for restricted longevity in those patients who survive appropriate surgical procedures upon the aorta.

Duodenal Ulcer

While one could continue into many other ramifications regarding coronary and associated diseases, I have chosen to conclude with the common problem of duodenal ulcer.

For clinicians I need not enlarge on the problem of myocardial infarction complicating the state of bleeding duodenal ulcer. Equally obvious is the problem of precipitation of duodenal hemorrhage by anticoagulant therapy for myocardial infarction.

The pathologic limitations to the treatment of coronary disease become less absolute with time. Yet a constant limitation among patients with varying manifestations of coronary disease is the ever present underlying lesion, the coronary atheroma, a lesion which, like the sword of Damocles, while not necessarily dropping, threatens to inflict its damage yet again.

Summary

Anatomic limitations in the treatment of coronary disease are relative to the state of development of medicine and to the facilities available for care of the patient.

Direct attack upon the underlying atheroma is limited from a dietary point of view and relatively limited from a surgical point of view by virtue of the usually extensive distribution of lesions.

In acute myocardial infarction, limitation depends upon the extent of loss of muscle and upon specific complications such as rupture of the heart.

In patients with healed myocardial infarction, therapy is limited by the extent of loss of muscle, either from the distribution of the healed infarcts or from the addition of a new acute infarct.

Many patients with coronary disease suffer from additional conditions which either alone or together with the coronary disease represent major barriers to success in therapy. Such conditions include hypertension, valvular disease, diabetes and myxedema.

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Suicide and Related Clinical Problems

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Although some individuals are prone to suicidal acts, it should initially be noted that the suicidal act itself may occur with multiple types of psychiatric diagnoses, or without any specific type. Degrees of depression vary from "depressive neurosis" to those of more psychotic proportions, such as manic-depressive illness, or "involutional melancholia," in which the suicide potential was once at a level where 25 percent of the patients died by their own hand.[3] Schizophrenic individuals may also manifest suicidal tendencies, particularly when they have prominent mood disturbances or delusional thoughts.

A further distinction is sometimes made between a genuine suicide attempt and a suicidal gesture. An operational definition of suicide would define it as "an act of self-destruction." It is an ultimate expression of the "acting out" of unconscious, self-destructive tendencies where the self is the object-victim. A suicide then combines an unconscious urge to kill, a desire to die, and also a wish to be killed; all are achieved in a "successfull" suicide.[6] Psychodynamically, a suicide externally expresses the intrapsychic hostile-aggressive forces *towards* the self which are literally and murderously acted out *against* the self.

The incidence of suicide is considered to be grossly underestimated by at least five to twenty times the reported figures. In 1964 the figure was 20,588.[2] Another interesting fact is that suicide is 2.5 times as frequent as homicide in the U. S. There are twelve times as many deaths by suicide as from aircraft accidents, a statistic which led someone to conclude facetiously that air travel is less hazardous than suicide. Suicide is ranked number five as the cause of death for white males between the ages of 15 and 44 years, and the incidence at age 50 is six times that at age 20. Below the age of 15 suicide is relatively rare; however, in both the 15 to 19, and the 20 to 24-year age groups, suicide is the fourth leading cause of death—

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after accidents, neoplasms, and homicide, with 600 deaths occurring annually in the two categories. Three of these four leading causes of death in these young age groups are seen to be related to problems in the realm of aggression. There are also over 100 suicides per year reported between the ages of 10 and 15, and about 10 per year under the age of 10.[9]

Descriptive Features in the Suicidally-Prone Individual

There are various types of clinical signs and symptoms to be kept in mind when the possibility of suicide is present. The first is evidence of a severe depressive mood state. Although there are "smiling" depressions, sadness in the patient is one of the best clues to a depressive state. Accompanying such a mood are references to discouragement, disillusionment, and disappointment. Disappointment includes reactions to frustrations and losses which may be peculiar to the individual, but are nevertheless significant for him, such as the loss of a job or other indices of his inadequacy, varying from social disappointments to sexual failures and impotencies. It is not true that a suicidal threat or gesture can be ignored or regarded as a "bluff." Preoccupation with thoughts of suicide is always in itself a disturbing sign of emotional conflict and an indication for appraisal.

The following are listed as indices of suicide potentiality; the more indices present, the higher the risk.

Early Morning Awakening

There may be a persistent pattern of early morning awakening, one to three hours earlier than the *previous* pattern for the individual, accompanied by a depressive mood.

Difficulty "Getting Going"

There is often difficulty "getting going," especially in the morning, with the individual feeling somewhat less depressed by late afternoon. He may report that he needs to "push" himself much more to get things done and that he feels more fatigued, although doing less. Increased irritability and indecisiveness add to this picture.

Lack of Interest

Lack of interest in things that were previously of great interest is another sign of the individual's inability to function in his customary manner. The greater the degree of this interest loss, the greater the suicidal potential.

Abrupt Improvement

An abrupt improvement for someone who has been seriously suicidal or depressed should be taken seriously, since this is the most dangerous time for a suicide attempt to occur. It is hypothesized that in the depths of a depression the individual is unable to mobilize himself sufficiently to carry out the suicidal act; hence, when his spirits suddenly improve, he has a much greater potential. It is as though he has suddenly come to a "solution" whereby he may solve his problems via a decision to take his life and end it all.

Progressive Withdrawal

A progressive pattern of withdrawal is related to a lack of interest, but also refers to an individual's losing contact with those to whom he has previously been attached. The greater the degree of such withdrawal, the more apt are the "signals" to be missed in an individual who is becoming deeply suicidal.

Inability to Verbalize

The less an individual is able to verbalize about his depression, the greater the suicidal risk. The nadir of despair is reached when he no longer feels it worthwhile to communicate that despair to others, resulting in his feeling progressively more and more isolated.

Sadness and Loneliness

The essence of a depression is a mood characterized by enduring feelings of sadness and loneliness. These may vary in degree from transient periods of feeling "blue" to profound despair wherein a sense of deep pessimism prevails since the future seems hopeless. Patterns of reiterating how deeply guilty and worthless one is, contrary to any objective external standard, may often be of delusional proportions, and are seen in depressions of psychotic dimensions. Delusions need not be confined to schizophrenia; a variety of them may be noted in severe depressions as well. A few types will be noted. One is the *somatic,* wherein there is a persistent belief that something is physically wrong, despite the absence of physical findings. In some cases there are physiological changes, such as abdominal pains, constipation, or bad breath. In severe cases, the delusions become so extreme as to include "intestines rotting," a head filled with cement, etc.

Nihilistic delusions* are similar but are externalized rather than confined to the body. There may be a persistent belief that a terrible disaster is inevitably going to occur, that the world is about to disappear, etc. Signs and expressions of not liking oneself may expand in a psychotic process to profound accusations of self-worthlessness out of proportion to any misconduct. Delusional *guilt* may be an accompaniment and expresses not only anticipation of punishment but a conviction of its desirability. The above may all lead to feelings of change in one's body or environment.

In these cases reassurance rarely has any significant effect. Giving these individuals "pep talks" or attempting to "talk them into" enjoying life rarely has more than a temporary effect. It may actually make them more depressed in some cases since it engenders a view that they are failing others' expectations of them as well as their own.

Psychodynamic Patterns in Suicide

In addition to the external features previously noted, there are motivational forces present. Herein lies the distinction between the *descriptive* and the *dynamic* aspects of psychiatry. The dynamics encompass various conflicting forces within an individual personality, coupled with some of the predisposing background factors which include his psychological and social development. The psychodynamic factors in a suicidal individual are concerned with some of the intricacies within him which lead him to contemplate suicide.

To formulate dynamics we must keep in mind the significant *details* of a suicidal act, the *method or technique* contemplated, as well as the *circumstances* which may induce an attempt.[4] As clinical examples of *details*, we may think of the case of a 45-year-old woman who, after receiving a letter that her son has been killed in the Armed Forces, jumps out of a window a month later with a picture of her son tucked inside of her dress, with the inscription: "Bobby, I'll see you soon." Another example is that of a 60-year-old man who is informed that he has cancer but fails to reveal the fact to his family. He commits a genuine suicidal act to "save" his family from having to see him die a long, painful death.

The *method* of suicide is important since it reveals information regarding the personality integration and functioning of an individual. We thus learn whether there have been multiple suicide attempts previously, whether they have been carried out in a planned, methodical manner, and whether there have been chaotic attempts which have miscarried. Several questions are relevant here. It is important to learn the patient's attitude toward death and what he thinks will follow death or a "successful suicide attempt," as well as his thoughts at the time of planning such an act, either then or at the time of any previous attempts. For example, "What were you thinking at the time you took the 20 seconal tablets?"

There are various psychodynamic constellations to be noted, with the warning that a patient cannot be automatically categorized; rather the individual conflicts and circumstances must be delineated in each separate case in order to reconstruct the motivations.

Getting Even

One type of psychodynamic formulation may be considered under the heading of "death as a getting-even maneuver." Let us consider the situation of a particular 17-year-old boy who has been rejected from a college which he has long been hoping to attend. His response is to shoot himself, in the conviction that he will actually die. The dynamics here consist of attaining an illusory control over the people and the situation which have rejected him. He is now the one in power. Such individuals visualize the suffering their demise will cause others, e.g., how their relatives will react when they see them lying in a coffin. This type of theme is frequently noted in adolescents in whom there is a prominent element of self-pity.

Gaining Power via Death

There is a second and related dynamic formulation which involves the "gaining of power via death." In this situation the individual attempting suicide has the ultimate control of deciding if he wishes to live or not, rather than leaving his life and fortunes at the disposal of others to decide. It is an effort to negate a feeling of being the helpless victim of others' decisions. In some cases it may take the form of outwitting fate.

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*See Test Your Word Score Page 1637.

Retroflexed Homicide

A third possibility is that of suicide as a "retroflexed homicide:" an inverted homicide, which Freud discussed in a 1917 paper, "Mourning and Melancholia."[5] An example is the wife of a middle-aged man who has been having an affair outside his marriage for five years. When she becomes aware of the situation and confronts him with making a choice, he decides to leave her for his paramour. At that point his wife attempts suicide. The dynamic meaning for this lady is to self-punitively act out her anger in an act of *self*-destruction in contrast to destroying her husband and/or his girl friend. The message is also, "Look what you have done." Some theorists maintain that this motive, along with other factors, is present in almost every suicide.

Reunion

A fourth theme is that of accomplishing a "reunion." In this type of situation the act of dying is used in an effort to reinstate a close relationship which had previously existed, such as with an individual now dead. The emphasis here is not on dying itself, but rather on the hoped-for reunion which is to follow. Consequently, in these cases there is often a pleasurable feeling, which can be noted in interviews with an individual as he talks nostalgically about his longings. Marked dependency needs are conspicuous in these people, particularly as directed towards parental figures or members of the family who have "deserted" them, by such acts as death, abandonment, or threatened divorce. An example would be a 35-year-old man whose wife had been killed in a car accident six months earlier and who finds himself repeatedly driving at 80 and 90 miles an hour on slippery highways. This behavior finally culminates in an almost fatal accident. The topic of "accident proneness" is relevant here. Another variation is the form of chronic suicide seen in alcoholism or addiction. A woman of 50 whose husband dies succeeds in becoming an alcoholic in a few years with all its concomitant self-destructive aspects.

Rebirth

"Death as a rebirth" is a fifth and related theme. This involves wishes to "start over" and is frequently verbalized to a physician once a relationship is established. It may be related to some loss or frustrating situation which the individual desires to "wipe out," such as a past misfortune or disappointment. Again, as with some of the other types noted, this is not really an effort to die, since the wish is to continue living but in a new form. It is a "death and transfiguration" theme. The magical or wish-fulfilling element is strikingly present with the denial of death as something permanent.

Self-punishment

A sixth formulation is that of suicide as self-punishment. This may be related to various themes where an individual regards himself as having failed and feels that a situation is irremediable. Such individuals often have exceedingly high and rigid standards for themselves: what we more technically term a "strict superego," with associated compulsive features. While this may account for the higher rate of suicide among physicians and certain professional groups than among the general population, it does not account for variations within the groups. The over-all annual rate for physicians has been estimated at 36 per 100,000, three times that of the general population.[1] However, among specialists there is a variation from a low of 10 per 100,000 for pediatricians to a high of 61 per 100,000 for psychiatrists if we presume the reporting to be accurate. When individuals with high standards fail to live up to those standards, an enormous amount of self-hatred is released. These individuals have a particularly predisposing background of depression-proneness in their personality.

In the past history there may be episodes when their aggression was externally directed, so that they are not aware of the depressive component within themselves. In extreme cases there may have been an integration on a paranoid level which succeeded in keeping their depression in abeyance. A variation of the self-punishment theme is a suicidal act with an element of atonement. Self-punishment has the added element of relieving one of guilt in the form of an expiation. Following a genuine suicidal effort, there is atonement for the failures, and the depression temporarily lifts. This is often surprising to some clinicians who cannot understand how an individual who has just done such an act can subsequently appear so tranquil and intact.

Schizophrenic Process

A more exotic suicide is seen in an individual who views himself as already dead even before the act of suicide. These individuals are often schizophrenic. They describe themselves as having already died or as feeling emotionally dead and detached. One is impressed by their flatness and lack of emotion. Death is viewed as a release from the suffering of life; suicide is merely putting the finishing touches on an event that has already occurred in their fantasies. One young adolescent lay in bed most of the day, after surviving a suicide attempt, with a cloth over his face, asserting that he was dead. This type of manifestation is part of the larger picture of the schizophrenic process.

Götterdämmerung

A wit once said: "Suicide is still a fatal disease." This is true for the acute attempt if successful, but it is just as true for more insidious acts which eventually culminate in self-harm. The varieties of behavior that can be described as small acts of self-destruction are almost limitless and include neglect of one's physical health, excessive types of risk-taking, and any self-defeating behavior in which strong, unconscious determinants lead an individual to destroy either those close to him or something to which he was once dedicated, such as a social goal, a reputation, a business, or a profession. In the latter case, the destruction may have dramatic overtones, such as a combined homicide-suicide (*a Götterdämmerung*), but it more frequently takes the form of undermining personal relationships, within a family or among a group of people. The concealment of strong paranoid and sadistic tendencies then becomes more evident, although it may not be noted until the long-range consequences of an individual's life are viewed in retrospect.

These various psychodynamic themes have alluded to the interpersonal elements involved in any suicidal act. These types of interactions are often present within a family unit, or among other individuals with whom a person is in contact prior to his suicidal act. In addition, interacting factors from the past seem to "live on" as though in a state of perpetual readiness and, under precipitating stresses, play an active part in any given suicidal act. Conveying covert or unconscious destructive wishes to another person is one of the more cogent forces operating in any type of acting-out behavior. Suicide and homicide are merely a sub-class of such communication of wishes. The following case illustrates this type of pattern.

A 28-year-old divorced, white male was found dead by hanging in an institutional setting. There had been a history of one suicide attempt previously for which he had been given electro-shock treatment, with several depressive episodes prior to his death. His behavior alternated between various forms of self-destruction activities, such as exhibitionism, for which he had been apprehended several times. During his institutional stay, his widowed mother had visited him several times and noted him to be deeply unhappy. After his suicide she related that during these visits she had begun to pray earnestly every night that if her son could not live outside an institution, God should release him by death from the burden of so living. Shortly after one discharge, he was again committed for similar behavior, and faced a long detention period. The mother's feelings were reinforced by her being told that no treatment was available for her son's condition. Realizing her own wish that her son not have to spend most of his life institutionalized, she literally conveyed this wish to him. At that time he agreed with her that such a meaningless existence would not be worth the effort. It was shortly thereafter that he was found dead. Related background factors operating in this materialization of a death wish have been omitted for brevity. It should be noted that in no way was the mother operating with a conscious wish to kill her son. It was rather the derivative, yet fully potent wish, which was transmitted and acted upon.

"Gestures"

"Gestures" are often distinguished from what are referred to as genuine "attempts." Such a dichotomy* introduces all types of fallacies, such as: "Even fakers have accidents." This undoubtedly does happen, but more important is the failure to understand the personal and social factors leading to such behavior. Characteristic of a gesture is an act which appears to have a self-destructive theme, but in which the observer can perceive a self-limiting quality such as, "He really didn't want to die." The examples vary from taking insufficient quantities of pills to engaging in risk-taking behavior after notifying someone with whom the "faker" is involved or to whom he is attached, or in wrist cutting. A host of responses may then arise in the clinician, varying from outright anger and rejection to a personal involvement amounting to a persistent type of rescue operation.[8] This is especially so if the perpetrator is an attractive and dependency-evoking female in the adolescent or young adult stage. A type of intense attachment with open displays of covert hostility is then reenacted—often with a succession of professional people in schools, agencies, clinics, and hospitals. Diagnostic labels become attached in transit, including "psychopath" (especially by older staff), "schizophrenia" (by middle-aged staff who are aware of the covert manifestations of ambulatory schizophrenia), "hysteria" (by young male staff), and "normal" (by those who see such gesturing behavior as a response to a disturbing environment and who are prone to label behavior as socially-determined).

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*See Test Your Word Score Page 1637.

There are often precipitating factors in such situations, such as a disorganized family structure, a background within the family where sensual and aggressive impulses were openly displayed with only a modicum of controls, alternations between indulgence coupled with unpredictable condemnation, and punishment for "acting so disgracefully." The primary defenses operating, besides acting out, appear to be a projection of problems on to others, as well as externalizing them, so that difficulties are viewed as impinging from outside sources rather than as self-imposed. Escapades of a sexual or drug-induced type have often been tried, as well as involvement in multiple efforts to make therapeutic contacts via group activities.

A "gesture" appears to be a reaction to frustration when these "outs" are either not available or have lost their vitality and appeal. The gesture then has a variety of meanings. It is not only attention-getting for secondary gain, but reinstates a dependency relationship where "somebody cares." It is simultaneously a direct form of impulse discharge, thus accounting for the observed relief or state of relaxation frequently following it. For some this is equivalent to a self-punitive purification process like any token of suffering. The anlage* is seen in young children who transgress and then ask to be punished or hit themselves. Acting-out gestures serve to avoid dealing with personal feelings and conflicts, since they are rather "put into action" instead. In the more disturbed, certain self-mutilative acts may accompany more bizarre trance states where altered consciousness may be present. These efforts may be not so much gestures as part of a ritualized delusional system.

Summary

Some of the more acute indicia of severe depression are handled on the basis of the *descriptive features* that are detectable from a clinical evaluation, and the *psychodynamic patterns* which deal with the conflicts and motivations with which an individual is struggling. The faces of depression, as well as of psychoses, are often masked, and exert profound effects not only on the individual but on all those with whom he comes in contact.

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*See Test Your Word Score Page 1637.

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Ideals

Ideals are to run races with. The moment we stop chasing them they sit down and become opinions.—Lutheran.

|| Thrombocytosis

A Clinical Evaluation of 322 Patients

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THROMBOCYTES WERE THE last of the cellular elements of the blood to be recognized, probably by Bizzozero[1] in 1882. They are still the most poorly studied of the formed elements in the blood. Many of the studies showing thrombocytosis associated with various pathological conditions were done at a time when indirect counting techniques were in use. Because of the poor reliability of these methods[2] and the fact that the mechanism of thrombocytosis in any given situation is not well understood, most of this early information has been ignored. However, recent investigators[3-5] have suggested a humoral mechanism for maintenance of normal platelet levels, and an excess of this humoral substance in disease states results in thrombocytosis.

The purpose of this paper is to call attention to the principle conditions in which elevated platelet counts are found. It also reemphasizes the need for a thorough evaluation of patients with thrombocytosis.

Materials

Records of the hematology laboratory at the Minneapolis Veterans Hospital, Minneapolis, Minnesota, for the period of one year were reviewed. Charts of the patients with platelet counts above 350,000/mm^3 of blood were studied. The highest platelet count in the clinical record was used in this study. The hemoglobin level at the time of the peak platelet count was also recorded. Evidence of thrombosis was obtained from review of the clinical records and autopsy reports if available. There were 12,557 hospital admissions during the year the study was undertaken.

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Method

The platelet count was done by the modified Rees-Ecker technique[6,7] with an ordinary light microscope.

The mean normal platelet count in this laboratory for males is 240,460 per mm^3 plus or minus two standard deviations of 93,707 (N=39) with a 95 per cent range of 146,000 to 335,000 per mm.[3] These values compare with a mean of 258,000 and a 95 per cent range of 130,000 to 380,000 (N–180) reported by Miale[8] and a narrower 95 per cent range than that of Brecher, Schneiderman, and Cronkite (140,000 to 440,000).[9]

Results

Three hundred and thirty-nine patients with platelet counts above 350,000 were found. This number represented a 2.57 per cent incidence of thrombocytosis when compared with the total number of hospital admissions. It must be pointed out that platelet counts were not done on every patient admitted to the hospital. Therefore the study cannot answer the question of true incidence, but it does allow an analysis of the kinds of disease associated with elevated platelet counts. The records of 17 of these patients were unobtainable. From the 322 records available, it was found that 206 patients had malignant disease and that 116 had benign diseases. Table 1 shows the malignant conditions associated with thrombocytosis.

Table 2 shows the cases of thrombocytosis associated with various benign diseases.

There were 38 cases with thromboembolic disease in the 322 cases studied. Thirty-two of the patients suffered from this complication after the thrombocytosis was discovered, while six had had thromboembolism in the past.

The average platelet counts with and without recent thrombosis were 539,000 and 497,000 respectively. Upon application of Student's "t" test the difference between these two values was not statistically significant ($0.1<p<0.2$); 9.9 per cent of the patients in this study developed thrombosis. When the platelet count was above 500,000, 11.5 per cent of the patients developed thrombosis, and when the platelet count was below 500,000, 8.9 per cent developed this complication. Table 3 summarizes the types of thromboembolism observed. The 32 patients with recent thrombosis had a total

TABLE 1

Thrombocytosis Associated with Malignancy
(206 Cases—64.0%)
Platelet Count in Thousands

Diagnosis	350 to 500	500 to 800	Greater than 800	Total
Carcinoma of lung	38	29	1	68
Carcinoma of colon and stomach	14	16	2	32
Lymphoma	12	6	—	18
Carcinoma of upper respiratory tract	6	8	2	16
Polycythemia	10	5	2	17
Carcinoma, site unknown	6	6	—	12
Carcinoma of urinary tract	7	4	—	11
Carcinoma of pancreas	4	1	—	5
Malignant melanoma	1	2	1	4
Miscellaneous malignant conditions	13	8	2	23
Totals	111	85	10	206

TABLE 2

Benign Conditions Associated with Thrombocytosis
(116 Cases—36.0%)
Platelet Count in Thousands

Diagnosis	350 to 500	500 to 800	Greater than 800	Total
Iron deficiency	12	5	—	17
Bleeding	13	2	—	15
Alcoholism and cirrhosis	9	3	—	12
Rheumatoid arthritis	3	6	1	10
Splenectomy	4	3	3	10
Pernicious anemia (post treatment)	5	—	—	5
Pulmonary tuberculosis	5	—	—	5
Miscellaneous conditions	29	12	1	42
Totals	80	31	5	116

TABLE 3

Recent Thromboembolic Conditions Associated with Thrombocytosis

Condition	Number of Instances
Pulmonary embolism	8
Thrombophlebitis	14
Cerebrovascular accident	8
Myocardial infarction	3
Other arterial thromboses	2

of 35 thromboembolic episodes. Twenty-five of the patients with thrombosis had malignant disease.

Of the 322 patients in this study, 88 (27.3 per cent) had a normal hemoglobin, i.e., above 14 grams per 100 ml. The Figure shows the hemoglobin concentrations in patients with and without thromboembolic disease. The average hemoglobin concentration in the group which developed thromboembolism was 13.6 grams per 100 ml, while the average hemoglobin concentrations of the group who did not develop this complication was 12.2 grams per 100 ml. When applying Student's "t" test, the difference between the average hemoglobin concentrations in patients with and without thrombosis was statistically significant ($p < 0.01$). In other words, the patients with thromboembolic complications had a significantly higher hemoglobin concentration.

The correlation between the hemoglobin concentration and platelet count in the entire series was investigated, and no significant correlation was found ($r = 0.0000$).

Discussion

Physiology

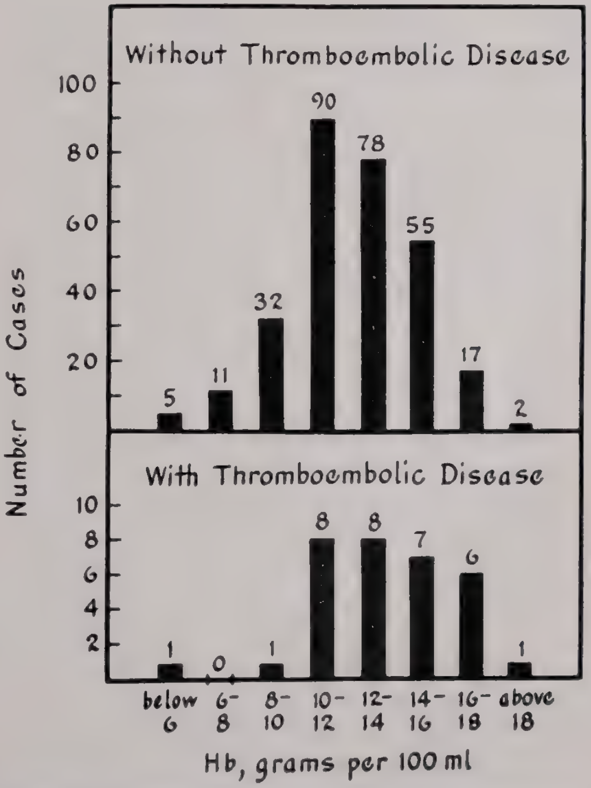
The physiological regulation of platelet production may include a humoral mechanism. Thus, under appropriate conditions plasma from both animals[5,10] and man[3-5,11-13] is capable of stimulating platelet production. Deficiency of platelet-stimulating plasma factor has been described in a child with congenital thrombocytopenia.* Increased amounts of platelet-stimulating plasma factor has been observed in animals made thrombocytopenic with platelet antisera.[10] In conditions with a temporary thrombocytopenia increased amounts of platelet-stimulating plasma factor have been recorded immediately before the rise in the platelets.[5]

Thrombocytosis in Malignant Disease

The most surprising result of this study was the high frequency of malignant disease among the patients with increased platelet counts. The association of thrombocytosis and cancer was first described by Riess in 1872.[14] Although at that time platelets were not considered cellular elements, this association was later confirmed by Hayem[15] in 1889. Subsequently, many investigators have found thrombocytosis in patients with various tumors.[16-24] The concept that the platelet counts fall in the late stages of tumor development is supported by occasional reports of thrombocytopenia in cancers.[25-28] Qualitative changes in the platelets have also been described in patients with malignancy.[22,23,29-31]

The mechanism of the thrombocytosis associated with cancer is not understood. It is not clear whether the thrombocytosis is related directly to an effect of the tumor or to some secondary effect, i.e., the anemia. It is unlikely that it is due entirely to the anemia as suggested by Noeff[19] because it appears in patients who are not anemic, and there is no statistical correlation between the hemoglobin concentration and the platelet count in the present study. Furthermore, thrombocytosis occurs with a high frequency in patients with tumors where bleeding is unusual, i.e., carcinoma of the lung.

The mechanism of thrombocytosis could be due to increased production of platelets or to a decreased rate of removal of circulating platelets. To our knowledge no studies have



Figure—Frequency of hemoglobin distribution in patients with and without thromboembolic disease.

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*See Test Your Word Score Page 1637.

been done which show prolonged survival of platelets in the circulation. Increased production of platelets could be due to increased activity of pre-existing megakaryocytes or to an increased number of megakaryocytes. Numerous workers[23,33-35] have shown an increase in the number of megakaryocytes in the bone marrow of cancer patients. Hueper[32] reported such an increase in spontaneous mammary cancers in mice. The present evidence would suggest over-production of platelets in malignancy.

Fanger, Cella and Litchman[36] reported two cases of cancer in a series of 28 cases of thrombocythemia; they postulated that the platelet elevation might be due to tumor necrosis. We have observed marked fluctuation in platelet counts but have been unable to correlate these with changes in tumor activity. There is no consistent rise in the platelet count with tumor necrosis from x-ray or chemotherapy. However, it is recognized that irradiation or chemotherapy suppresses the bone marrow response.

Thromboembolism

It is generally believed that there is an increase in the incidence of thromboembolic disease among patients with carcinoma. This increase has been somewhat difficult to define because the cancer patients frequently have other factors, i.e., inactivity, debility, surgery, and prolonged bed rest, which are known to be associated with an increased incidence of thromboembolic disease. This disease is frequently observed in patients with carcinoma of the pancreas. Gullick[37] reported 17 cases of thrombophlebitis in 68 cases of carcinoma of the pancreas. Thrombophlebitis may be the presenting symptom in patients with carcinoma of the lung.[38] Sproul[39] found a 2.5 percent incidence of venous thrombosis in patients with carcinoma of the lung.

In the present study the difference between the average platelet counts in patients with and without thrombosis was not statistically significant, a fact which may be due to the skewed frequency distribution of our data.[40] However, it should be remembered that only cases with platelet counts above the normal range were included in this series.

The question arose whether the hemoglobin concentration also might be a factor in the development of thrombosis. A statistically significant direct correlation between hemoglobin concentration and thromboembolic complications has been described in this paper. This concept is supported by Nordoy[41] in his experimental studies in rats.

Thrombocytosis in Acute Blood Loss and Iron Deficiency

Acute bleeding and chronic iron deficiency was documented in 32 patients with thrombocytosis in this study. It is well known that acute bleeding is followed by thrombocytosis.[42,43] It is less well known, however, that thrombocytopenia may precede this thrombocytosis. Thus, Desforges, Bigelow, and Chalmers,[42] studying acute gastrointestinal bleeding, found that the platelet count fell during the bleeding and that it subsequently rose, frequently to levels above normal in the convalescent period, reaching a peak seven to 14 days after the bleeding episode. Numerous workers[2,14,15,44-46] have called attention to elevated platelet counts accompanying chronic iron deficiency anemia with and without hemorrhage. The elevated platelet counts returned to normal following treatment of the iron deficiency.[45,46]

Surgery and Splenectomy

Several investigators[47,48] have demonstrated changes in the platelet count following surgery, similar to those seen after an acute bleeding episode. These changes are apparently not related to the degree of blood loss. The thrombocytosis is more prolonged and more pronounced after splenectomy.[2,49] One of the patients in this study had platelet counts ranging from 400,000 to 600,000/mm^3 20 years after splenectomy.

Rheumatoid Arthritis

Ten patients in this study with rheumatoid arthritis showed elevated platelet counts, a finding also noted by Levin and Conley.[24] Iron deficiency is quite common in this illness and may contribute to the thrombocytosis.[50]

Alcoholism and Cirrhosis

The usual problem encountered in patients with chronic alcoholism and cirrhosis is thrombocytopenia. In this study there were 12 patients with elevated platelet counts associated with cirrhosis or chronic alcoholism. Reasons for these elevations cannot be determined from the present study; however, three possible explanations should be considered. It is known from the work of Herbert[51] that thrombocytosis may occur in response to dietary folic acid. Since patients with alcoholism and cirrhosis of the liver frequently have folic acid deficiency,[52] response to this substance in the normal hospital diet may account for the observed thrombocytosis in some patients. Rebound thrombocytosis following thrombocytopenia may also occur on withdrawal from alcohol.[53] Another possibility is a subclinical iron deficiency of these subjects.

Pernicious Anemia

The thrombocytosis of pernicious anemia which occurs in response to specific therapy is also a well known phenomenon[54] and was observed in five patients. "Spontaneous remission" of pernicious anemia has also been associated with thrombocytosis.[18]

Infections

Several investigators[14-18] have found elevated platelet counts in patients with acute and chronic infection, especially tuberculosis. The mechanism of the thrombocytosis in these instances is not understood. It is not always associated with anemia. Port and Akiyama[17] observed a fall in the platelets during acute infection with a subsequent rise, frequently to a level above normal, following the crisis.

Miscellaneous Benign Condition

In most instances, these patients had only a single platelet count performed and no further evaluation was undertaken. It was this lack of further study that probably prevented us from placing these cases in a defined category.

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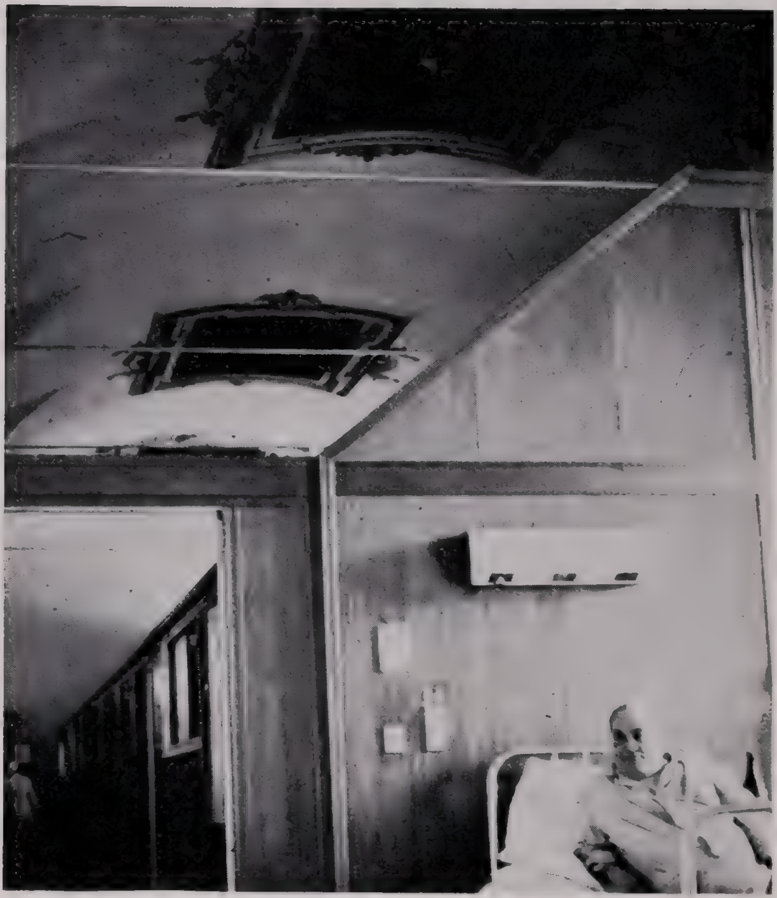
Thought

It was the habit of Immanuel Kant, famous German philosopher, to rise in the morning at five o'clock and think for two hours. He had no apparatus; there was nothing in his hands. He sat and thought; he did not just sit.—William Lyon Phelps.

Old Hospitals



Ospedale Fatebenefratelli, Rome

The Brothers of the Order of St. John of God faced an unusual problem when they modernized the ancient Hospital of St. John Calibita in Rome. The hospital, founded in 1575, is the headquarters of the order which operates 240 hospitals around the world. Its high-ceilinged Great Hall of the Sick was a model facility in the fifteen hundreds, but appealed little to twentieth-century patients who demanded more privacy than could be provided within its great expanse. The government decreed that the building was of historic and artistic significance and that its external appearance could not be changed. Furthermore, the Brothers were forbidden to add a second story inside the building or in any way to alter or obscure the venerable paintings which decorated the ceiling. Their imaginative architectural solution was the maze of paneled enclosures shown above. Each compartment accommodates five patients and is open at the top, affording a view of the ancient decorated ceiling. The sanctuary at the end of the church-like Great Hall has been converted into a television lounge.

Newer additions to the 280-bed voluntary hospital house departments of cobalt therapy, diagnostic isotopes, angiography and inhalation therapy. Most patients are covered by health insurance, and room rates for a five-bed room are 3000 lire ($4.80) per day. The Brothers' nickname, "do-good brothers", accounts for the popular name of the hospital which is Ospedale Fatebenefratelli.

Warren L. Kump, M.D.
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Brother Flavian Keane, O. H., Ospedale Fatebenefratelli: Personal Communication.

Tussive Syncope

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Tussive syncope is a loss of consciousness following an episode of coughing. Synonyms for this syndrome are "cough syncope" and "laryngeal vertigo."[1,2]

Credit for the first reported case of tussive syncope goes to Jean Martin Charcot, who presented two cases in November 1876; but much earlier Sydenham and Heberden described cases which may well have been examples of tussive syncope.[1,3,4]

Observations on Mayo Clinic Cases

Tussive syncope was diagnosed in 18 patients (16 males and two females) at the Mayo Clinic from 1950 to 1967. The patients' ages varied from 16 to 75 years with a mean age of 52 years. Twelve were cigarette smokers who smoked one to three packs per day and had a chronic, productive cough, with the syncopal spells occurring with paroxysms of coughing.

One of the six patients with no history of smoking had undergone resection for tuberculosis; he continued to have a chronic nonproductive cough related to empyema. Five of the patients who did not smoke had chronic asthmatic bronchitis with paroxysms of coughing associated with wheezing; eight gave a history of excessive intake of ethanol.

Tussive syncopal spells varied from 30 days to four years and lasted from 30 seconds to three minutes. Fourteen patients were obese; the body build of four was normal. Four patients appeared plethoric; 10 had inspiratory and expiratory wheezes and expiratory slowing. Three of the 18 patients had diffuse atherosclerotic changes, severest in the aortoiliac system.

Neurologic testing of 17 patients gave normal results.

Bronchoscopy showed chronic bronchitis in five patients, a deformity in the right mainstem bronchus in the patient who had undergone resection for tuberculosis, an obstructing

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†Mayo Clinic and Mayo Foundation: Section of Medicine.

carcinoma in one patient, and normal findings in the remaining 11 patients.

Roentgenograms of the thorax showed evidence of mediastinal widening from lymphoma in three patients, obstructive pneumonitis with a hilar mass in two, changes compatible with emphysema in two, and empyema in one patient; those of the other eight patients did not show any evidence of abnormality.

Electroencephalograms were made for eight of the 18 patients but were helpful only in a negative sense in that they excluded disease of the central nervous system as a cause of the syncopal spells. Only one of the 18 patients was polycythemic.*

Pulmonary function tests were performed in seven of the 18 patients; they demonstrated an obstructive pattern in six patients and a normal pulmonary function in one patient. Pulmonary function in one case is demonstrated (Tables 1 and 2), showing a mild obstruction component as well as a greater-than-normal pulmonary resistance and maximal expiratory pressure.

Clinical Characteristics of the Syndrome

The syndrome of tussive syncope occurs predominantly in men, and in one series, 97% of the patients were males. In this series, the syndrome occurred most frequently among patients between the ages of 35 and 60 years, with the peak incidence occurring in the 40s.[1]

Respiratory Disorders

The typical patient frequently has a mild chronic respiratory disorder, the commonest disorders being chronic bronchitis, emphysema, and bronchial asthma. He is obese, of heavy musculature with a large chest, plethoric, robust, and a creature of excesses. Usually he has a history of excessive smoking and excessive ingestion of alcohol. Attacks frequently occur during eating, drinking, or laughing.

Orthostatic Effect

Position tends to affect the occurrence of syncope; therefore attacks occur most frequently when the patient is in a standing position, although they may occur in any position. The cough is typically dry, paroxysmal, and nonproductive. Patients may frequently be hypertensive and have evidence of peripheral vascular disease. In scattered reports the syndrome has been associated with gout and other rheumatic symptoms.[1,2,5]

Typical Attack[3]

The patient exhibits a coughing paroxysm and his face becomes congested. Several seconds after onset the eyes become fixed and vision becomes less acute with loss of peripheral vision; the patient is able to hear commands but is unable to respond. If cough ceases at this point, signs and symptoms do not progress; if cough continues, however, within a second or two the eyes turn upward, consciousness is lost, and the patient becomes flaccid. Cough ceases with the loss of consciousness.

The attack may rarely be accompanied by mild convulsions; but tongue biting and incontinence do not occur. If clonic twitchings develop, they occur about two seconds after the loss of consciousness and usually involve the orbicularis oris and hand muscles. Consciousness is regained within about 10 seconds. Duration of the attack is characteristically two to 10 seconds, but may be 30 seconds to one minute.[1,2]

Etiologic Aspects

The three types of etiologic mechanisms: hemodynamic, reflex, and "concussive" are thought to be operative in tussive syncope.[6] It is probable that any one of these three mechanisms, or any combination, may be responsible in any individual case.

Hemodynamic

Basic to each of these three mechanisms is a modified Valsalva maneuver. In performing a Valsalva maneuver, the glottis is voluntarily closed and a strong expiratory effort is made against the closed glottis. This action may produce an intrathoracic pressure in excess of 80 mm Hg. The pressure is reflected in a similar rise in the alveoli, blood vessels, and other structures in the thorax as well as increased intra-abdominal pressure caused by the action of the abdominal musculature.

The main hemodynamic effect of the Valsalva maneuver is impedance of the return of blood to the right side of the heart. Therefore, venous pressure in the head and extremities increases sharply, venous return decreases sharply, and cardiac output and arterial blood pressure also decrease. As a result of blood flow in the sino-aortic zones, the heart rate increases.

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*See Test Your Word Score Page 1637.

TABLE 1

Pulmonary Function

	Estimated normal	Before treatment	After treatment with Isuprel
Pulmonary volumes			
Vital capacity (expiratory), L	4.3	4.79	5.16
Inspiratory vital capacity, L	4.3		
Residual volume, L	1.5	3.86	
Total capacity, L	5.8	8.65	
RV/TC × 100, %	<30	45	
Functional residual capacity, L	2.6	4.28	
Expiratory reserve, L	1.1	0.42	
Maximal breathing capacity, L/min	145	106	118
Maximal midexpiratory flow, L/sec	>2.5	1.5	2.0
Expiratory slowing, grade	0	2	1
Nitrogen washout index, %	<2.5–2.5	0.9	
Arterial oxygen saturation, % (oximeter)			
Resting (air)	95–98	98	
Resting (oxygen)	100	100	
Before exercise (air)	95–98	99	
Exercise (air), 3.0 min	No fall	99	
Exercise (oxygen), 3.0 min	100		
Ventilation (sitting rest, breathing O_2)			
L/min		13.81	
Rate: respirations/min		13	
Average—tidal volume, ml		1,062	

TABLE 2

Special Studies of Lung Mechanics

	Observed	Predicted
Compliance, L/cm		
Dynamic (quiet breathing)	0.209	0.260 ± 0.06
Static	0.455	
Retractive force at total capacity, cm H_2O	–32.0	–30 ± 7.5
Pulmonary flow resistance, cm/L/sec	6.23	2.56 ± 0 6
Maximal expiratory pressure, cm H_2O	200.0	98 ± 35
Maximal inspiratory pressure, cm H_2O	–56.0	–35 ± 10
Cough pressure, cm H_2O	235.0	Male 200 ± 50 Female 150 ± 30
Slope of flow-volume plot	0.909	2.7 ± 0.8
Peak expiratory flow, L/sec	5.51	5–8
Peak inspiratory flow, L/sec	5.01	4–8
Total lung capacity	6.90	5.8
1/slope of flow-volume plot	1.10	
Vital capacity (inspiratory), L	4.82	4.3

As soon as expiratory effort is decreased, blood rushes into the right ventricle, which becomes enlarged and contracts forcibly to pump its contents through the pulmonary circulation and into the left side of the heart. The surge of blood into the left ventricle causes a sudden increase in the systemic blood volume along with a rise of arterial pressure. This action elicits, reflexly from the pressoreceptors, a brief period of bradycardia, after which the pre-Valsalva conditions are reestablished.[7-9]

Reflex Mechanism

The major reflex mechanisms proposed to contribute to the production of syncope are all mediated via the vagus nerve. Vasovagal syncope is an entity caused by sudden reflex loss of peripheral resistance with resultant vasodepression and cardio-inhibition.

The various receptors involved in vasovagal syncope are (1) the carotid sinus (cardio-inhibitory, vasodepressor, and central), (2) the aortic pressoreceptors, (3) the pulmonary vessel pressoreceptors with increased pressure in the pulmonary circuit which causes bradycardia and hypotension, (4) the coronary reflexes (chemoreceptors), (5) the intracardiac baroreceptors, and (6) the cerebral pressoreceptors. All these reflexes will cause bradycardia and hypotension.[1,20-26]

Concussive

Coughing consists of four phases:[10] (1) inspiration, (2) sudden violent contraction of abdominal and accessory respiratory muscles, (3) a forceful explosive expiration against a closed glottis, and (4) with either a single severe cough or paroxysm of cough, a prolonged inspiration with some degree of obstruction.

A single cough can increase intrathoracic pressure 20 to 30 mm Hg; a more vigorous cough can increase it to 100 mm Hg. The cough associated with syncope will generally produce a pressure of 150 to 300 mm Hg. Hemodynamic effects are proportionate to the violence and duration of coughing attacks.[11,12,13]

Physiologic Changes

The consequences[14] of the Valsalva maneuver or of the cough[14] that is capable of producing syncope are: (1) peripheral vasodilation, (2) pulmonary vasoconstriction, (3) decreased venous return, (4) reflex bradycardia, (5) collapse of veins at the entrance of the thorax, (6) anoxemia, and (7) cerebral "concussion."

In one of our patients a sinus tachycardia and slight rise in blood pressure developed consistently with each period of unconsciousness.

Increase in cerebrospinal fluid pressure is essentially the same as the increase in intrathoracic pressure.[3,15] Sometimes the intrathoracic and cerebrospinal fluid pressures approach 300 mm Hg. Myelograms taken during the Valsalva maneuver show that when intra-abdominal pressure increases, the subarachnoid space narrows and the nerve roots are displaced medially.[3] Therefore, the increased intrathoracic pressure produces an enlargement of the epidural space and an increase in spinal fluid pressure. The increase of epidural mass is thought to be the result of engorgement of epidural veins caused by displacement of blood from the abdomen and thorax. The movement of loose fatty and areolar tissue and nerve roots into the spinal canal may add to compression of the subarachnoid space. Increase of the intracavitary pressure associated with cough might mechanically "squeeze" blood from both arteries and veins in such cavities to regions not subjected to increased extravascular pressure. These regions would be the skin and muscles of the head, neck, and extremities. The brain is essentially "bloodless."

Net Intracavity Pressure

The crucial factor is "net" intracavitary pressure (that is, intrathoracic, intra-abdominal, and intracranial pressures), which is the peripheral arterial pressure minus the increase in intracavitary pressure. In people with tussive syncope, this can approach or equal zero. Intracavitary vessels collapse and cerebral anoxia and syncope occur.[16] Females apparently can seldom cough forcefully enough to reach such pressures, which accounts for the greater incidence of tussive syncope among males.

Blood is "squeezed" from the cranium by the jugular veins and anastomotic channels of the diploic, emissary, and ophthalmic veins. A rich anastomosis exists between the intradural and the extradural veins. The rich venous plexus, including vertebral veins, serves as a reservoir to help maintain equilibrium between changes of pressure of cerebrospinal fluid and the cerebrovascular system. An increased cerebrospinal fluid pressure would result in an expulsion of blood from intracranial vessels to that part of the reservoir not subject to a similar rise in pressure.[3]

Increased Cerebrospinal Fluid

Another proposed central nervous system mechanism, more directly representing concussion, has to do with a sudden depolarization of cerebral cells due to increased cerebrospinal fluid pressure. However, certain investigators feel that the necessary elevated and sustained pressures are not feasible because of the vascular anastomotic channels that may act as escape valves.[17-19]

Emphysema

Emphysematous patients seem to have several predisposing factors for syncope.[27] Their alveolar pressure is greater than normal, and hence an even higher pressure may develop during coughing. They also have greater variations of intrapleural pressure. The increased rigidity of peripheral alveoli that accompanies the early loss of elasticity prevents full transmission of pressure from within the tracheobronchial tree to the pleural spaces, setting up a pressure gradient. The alveoli of these patients have an oxygen content lower than normal.[1,27]

Tussive syncope rarely develops in patients with large quantities of sputum. For some reason their intrathoracic pressure rarely exceeds 100 mm Hg.

Electroencephalographic changes may occur during cough syncope. The commoner patterns are slowing of dominant rhythms, increase in amplitude, and several seconds of electric silence.[16,28]

A recent report[29] on 14 patients with tussive syncope showed that half of them had demonstrable cerebrovascular disease. Poor cerebral circulation would serve to amplify the previously mentioned hemodynamic effects of forceful cough.[30]

Tussive syncope is more likely to develop in obese patients than in those of normal weight because obese patients have a low intra-abdominal pressure and, therefore, less blood flow from the abdomen to the chest.[7]

Summary

The basic mechanism of tussive syncope probably is a combination of decreased cardiac output, hypotension, decreased cerebral blood flow, and anoxia. Variable roles may be played by vasovagal reflexes, hyperventilation, and neuronal depolarization.

The mechanism must vary in different individuals as shown in one of our patients who consistently had tachycardia with slight elevation in blood pressure during repeated episodes of unconsciousness.

Tussive syncope is usually a self-limited, benign disorder. Treatment includes stopping smoking and drinking alcohol, and correction of obesity. An attempt may be made to suppress coughing and to liquefy secretions with high intake of fluids.

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Never do a wrong thing to make a friend or to keep one.—Robert E. Lee.

Edward Gibbon's Hydrocele

For many years it has been taught—I have taught it myself to generations of students—that Gibbon's hydrocele surpassed in greatness all other hydroceles, that it contained twelve pints of fluid, and that it was, in short, one of those monstrous things which exist mainly in romance.

What do we really know about it?

The first hint of trouble given by the hydrocele occurs in a letter by Gibbon to his friend Lord Sheffield. It is so delicious, so typical of the eighteenth century that I cannot resist re-telling it. Two days before, he has hinted to his friend that he was rather unwell; now he modestly draws the veil. "Have you never observed, through my inexpressibles, a large prominency circa genitalia, which, as it was not very painful and very little troublesome, I had strangely neglected for many years?"

Gibbon had been staying at the Sheffield House in the preceding June and his friends all noted that "Mr. G." had become strangely loath to take exercise and very inert in his movements. Indeed, he had detained the house-party in the house during lovely days while he orated to them on the folly of unnecessary exertion. It is an instance of how little we see ourselves as others see us that this supremely able man lived for years with a hydrocele that reached below his knees while he wore the tight breeches of the eighteenth century and was in the fond delusion that nobody else knew anything about it.

After leaving Sheffield House the hydrocele suddenly increased, as Gibbon himself says, "most stupendously;" and it began to dawn upon him that it "ought to be diminished." So he called upon Dr. Walter Farquhar; and Dr. Farquhar was very serious and called in Dr. Cline, "a surgeon of the first eminence," both of whom "viewed it and palped it" and pronounced it a hydrocele. Mr. Gibbon, with his usual good sense and calm mind, prepared to face the necessary "operation" and a future prospect of wearing a truss which Dr. Cline intended to order for him. In the meantime he was to crawl about with some labour and "much indecency," and he prayed Lord Sheffield to "varnish the business with the ladies," as if anything could any longer conceal the existence of this monstrous chimera.

He was tapped for the hydrocele; four quarts of fluid were removed, the swelling was diminished to nearly half its size, and the remaining part was a "soft irregular mass." Evidently there was more there than a simple hydrocele, and straightway it began to refill so rapidly that they had to agree to re-tap it in a fortnight.

The fortnight passed, and the second tapping took place, "much longer, more searching, and more painful" than before, though only three quarts of fluid were removed. . . . A few days later he was in great pain and moved with difficulty, the swelling again increased enormously, inflammation set in, and he became fevered.

Cline again tapped him and got away six quarts. Two days later he felt fairly well except for an occasional pain in his stomach, and he told some of his friends that he thought he might probably live for twenty years. That night he had great pain, and got his valet to apply hot napkins to his abdomen; he felt that he wished to vomit. At four in the morning his pain became much easier, and at eight he was able to rise unaided; but by nine he was glad to get back into bed. By eleven he was speechless and obviously dying, and by 1 p.m. he was dead.*

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*C. MacLaurin: Post Mortems of Mere Mortals, 1925.

Editor's Note: Probably the tranquilizing euphoria of impending death. Poor fellow probably had a hydrocele and incarcerated hernia which became strangulated with the usual sequela of unattended strangulation.

Massive Diffuse Hypergammaglobulinemia

Its Diagnostic Significance

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THE PURPOSE of this report is to delineate pathologic conditions in which a considerable degree of hypergammaglobulinemia may exist.

Quantitative determination of serum protein fractions by paper electrophoresis is rather frequently carried out with the hope of obtaining a clue of diagnostic importance. But unfortunately in the majority of cases knowledge of the quantitative distribution of the serum protein fractions adds little to the process of diagnosis. Electrophoresis of serum proteins is a convenient method to demonstrate the presence of various hypogammaglobulinemic conditions. Hypogammaglobulinemia is now known to be an abnormality which is common to a number of immunologic deficiency syndromes, and which requires further study of the patient.[1]

There are a few additional electrophoretic patterns of particular significance, such as the characteristic homogeneous narrow protein peaks representative of the paraproteins which may be associated with multiple myeloma, Waldenström's macroglobulinemia, and benign monoclonal gammopathies.† Nephrotic syndromes also are frequently associated with a characteristic pattern of the serum protein electrophorogram.

In most illnesses, however, the changes of the serum protein fractions are "nonspecific", i.e., the electrophoretic patterns combine one or more of three changes: decreased concentration of albumin, increased amounts of α_2-globulins, and abnormally high concentrations of γ-globulins.

Several comprehensive studies of the various serum protein alterations which occur in many pathologic conditions are available, and the interested reader is referred to them.[2-4]

Material and Methods

Among 2,000 serum protein electrophoretic patterns taken at random, 112 patterns were found which had γ-globulin concentrations of 1.6 or more gm/100 ml serum. This pilot study naturally suggested that massive hypergamma-

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*Mayo Clinic and Mayo Foundation: Section of Medicine.
†See Test Your Word Score Page 1637.

globulinemia was associated with only a limited number of clinical entities.

Several more thousands of electrophoretic patterns were then reviewed, and 40 instances in which the γ-globulin fraction measured 3 or more gm/100 ml were selected. The clinical diagnoses were obtained subsequently from the records of these 40 patients. The method of electrophoresis used at the Mayo Clinic for measurement of serum protein fractions has been described before.[5]

Findings

The diagnostic categories which were found in association with γ-globulin concentrations of 3 or more gm/100 ml of serum are listed in the Table.

Comments

The finding of massive hypergammaglobulinemia is of clinical importance to the practicing physician, for this protein abnormality considerably limits the number of diagnostic possibilities.

Usually multiple myeloma and Waldenström's macroglobulinemia are readily recognized by the narrow tall peak in the electrophoretic pattern, though further diagnostic procedures are required to differentiate the two conditions from each other.

After elimination of these plasma-cell dyscrasias by their recognizable paraprotein peak, there remain a limited number of conditions in which the pattern of the augmented γ-globulin has a broad diffuse shape. Conditions with massive diffuse hypergammaglobulinemia (3 or more gm/100 ml) include: (1) collagen diseases such as disseminated lupus erythematosus, scleroderma, Sjögren's disease, and rheumatoid arthritis (especially when taking the clinical form of Felty's syndrome); (2) sarcoidosis; (3) purpura hyperglobulinemica; (4) malignant lymphoma; (5) hepatic cirrhosis of the postnecrotic type, the type associated with chronic ulcerative colitis, and the type associated with porphyria cutanea tarda.

It is noteworthy that in this series no instance of a chronic infectious disease was encountered. This has practical significance, since fevers of undetermined etiology are particularly challenging to the diagnostician;[6,7] and the detection of massive diffuse hypergammaglobulinemia has been of help in the evaluation of some patients with fever of undetermined etiology. The finding of massive diffuse hypergammaglobulinemia in patients with perplexing fever warrants a further concerted effort toward the diagnosis of an underlying collagen disease or an occult lymphoma rather than an infectious process.

Of course, many patients having diseases of the above diagnostic categories never develop the degree of hypergammaglobulinemia review-

TABLE

Clinical Conditions Associated With Massive Hypergammaglobulinemia (3 or more gm/100 ml serum)

Clinical entities	γ-Globulin, gm/100 ml serum					Total Cases
	>7	6-7	5-6	4-5	3-4	
Multiple myeloma	3	1	3	7	1	15
Macroglobulinemia of Waldenström		1				1
Lupus erythematosus	1	1*		1*	2	5
Sjögren's syndrome	1				1	2
Scleroderma					2	2
Rheumatoid arthritis (Felty's syndrome)					2	2
Sarcoidosis					1	1
Purpura hyperglobulinemic					2	2
Lymphocytic lymphoma					2	2
Liver cirrhosis						
Postnecrotic				2	4	6
Chronic ulcerative colitis					1	1
Porphyria cutanea tarda					1	1
						40

*Lupoid hepatitis.

ed in this study.

Lymphogranuloma venereum, kala-azar, and visceral larva migrans are also rare conditions in which the serum γ-globulin concentration may be strikingly elevated;[8] but they were not encountered in the present series.

It should be emphasized that thousands of electrophoretic patterns were reviewed to obtain the 40 cases which were further analyzed, which indicates that massive hypergammaglobulinemia is a rare finding. On the other hand, when present it is of definite diagnostic help.

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Robert W. Schulz, M.D.

The cover slide was taken in the fall of 1967 on the beach of Dr. Schulz's summer home property. It is a view of the lagoon on Madeline Island looking toward the recently developed Big Bay State Park.

It was taken with an Exakta VX1000 on Kodachrome II and early in the morning for lighting effects. Doctor Schulz graduated from the University of Minnesota Medical School and interned at St. Luke's Hospital in Duluth. He is in solo general practice in his fourteenth year in Fairmont.

In addition to photography, Dr. and Mrs. Schulz raise and show Irish setters and presently are raising and showing American saddlebred horses.

School of Salernum

She that hath hap a husband bad to bury,
And is therefore in heart not sad, but merry,
Yet if in shew good manners shee will keepe,
Onyons and Mustard-seed will make her weepe.

Regimen Sanitatis Salerni

Editor's Note: Speaking of onions and mustard seed: the School suggests that if a woman has to bury a husband she doesn't really love and is glad to get rid of, she can use onions and mustard seed to make her tears flow copiously—for the sake of appearance. How about that for resourcefulness?

Viscerospinal Syndrome

This syndrome consists of visceral disturbances resulting from irritation of the spinal roots and sympathetic nerves at various levels. Ussher in 1933 first described this concept of visceromotor and sensory changes in relation to deranged spinal structures as a visceral counterpart to Dejerine's radicular syndrome.

As described by Ussher there are three components to the syndrome: (1) cutaneous, muscular, or articular foci of spinal irritability; (2) peripheral sensory and motor mechanisms, the former including cutaneous hyperesthesia and intercostal neuritis, and the latter including muscle spasm or atony and vasomotor changes; and (3) viscerosensory component with pain, often the result of motor activity, and a visceromotor component including bronchospasm, ureteral stricture, pylorospasm, and hyperperistalsis. The viscera involved depend upon the level of the spinal cord affected.

Fatigue or acute increase in muscle tone are factors in aggravating peripheral symptoms. Correction of physiologic derangement or mechanical abnormalities, such as scoliosis of the spine or an articular facet defect, are reported by Ussher to yield surprisingly good results in many instances.

Durham, Robert H.—Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York

Centenarians

Of recent years physiologists have bestowed much attention on centenarianism, but only to find how elusive the problem is. Race does not solve it, nor climate, nor heredity, nor even careful living. Centenarianism is to be met with everywhere, and under the most diverse conditions. A scientific investigation of authentic cases, however, has proved that plain living, fresh air, recreation, and abstinence from strong drink and tobacco are important causes of the extreme prolongation of human life.

Adam, when he pleaded with Orlando to be allowed to become his servant and feared rejection on the ground of age, had the root of the matter in him.

> Though I look old, yet I am strong and lusty;
> For in my youth I never did apply
> Hot and rebellious liquors in my blood,
> Nor did not with unbashful forehead woo
> The means of weakness and debility;
> Therefore my age is as a lusty winter,
> Frosty, but kindly.

But if we do not know all the factors that make for an abnormally long life, and find it impossible to fix the relative values of those that are ascertainable, it is at all events open to us to study the lives of centenarians that have been publicly recorded, in order to discover what manner of men they were, how they lived, and worked, and passed the allotted span without the eye becoming dim or the natural force abated. By following their precepts, and taking stock of their habits, we, too, perchance, may live to the proverbial green old age, conditionally, of course, that we start the race of life with a sound constitution, and run it under circumstances similar to theirs—two not unimportant qualifications.*

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*W. Forbes Gray: Five Score, 1931.

Hematologic Toxicity of Chloramphenicol.

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An almost uniformly fatal aplastic anemia and the subsequent development of leukemia in patients treated with chloramphenicol emphasize the necessity for a careful, conservative approach when this drug is prescribed.

Two case reports will serve to highlight the pathogenesis, magnitude, clinical features and therapy presented by the infrequent patient who reacts so unfavorably to this antibiotic.

The introduction of chloramphenicol in 1947 was quickly followed by extensive use because of its high degree of efficacy with a wide range of infections and its apparent lack of toxicity. Originally obtained from a Streptomyces fermentation process, it was later synthesized and its chemical structure defined (Figure). The presence of the nitrobenzene ring and its potential toxicity was noted by Dr. J. E. Smadel.[1] However, in his large experience with the early use of chloramphenicol no toxicity was observed. The earliest report of hematological toxicity was by Volini et al. in 1950.[2] Fatal cases were first reported by Rich et al. in 1950[3] and, in 1952, by Loyd's report of fatalities.[4] Following the report of 24 cases of aplastic anemia associated with chloramphenicol administration,[5-10] 21 of which were fatal, the Food and Drug Administration[11] reviewed the drug, and a warning of hematologic toxicity was required of the manufacturer. Reports of toxicity then declined sharply. The decline was brief, however, and 83 fatal cases were reported in 1959 alone.[12] Since that date the American Medical Association registry on adverse drug reactions has reported a steady decline in the annual number.[27]

Case Reports

Case 1

A 45-year-old Caucasian female was admitted to Minneapolis Veterans Administration Hospital on 1/16/66 for intractable vaginal bleeding since 1/7/66. The patient had been treated by her private physician during the summer and fall of 1965 for an otitis media with penicillin and then, following cultures, with chloramphenicol. She took approximately 250 mgm. of the drug every four hours for six days in July. A three-day course of 250 mgm. every four hours was given 9/22/65 and repeated on 10/2/65. The patient related that she may have had the prescription refilled after this. Thus the total dose was in the range of 12-15 grams of chloramphenicol.

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The patient had a normal menstrual period on 12/20/65, but on 1/7/66 excessive vaginal bleeding appeared and continued. On 1/11/66 she was hospitalized by her physician. A hemoglobin was 10.2 gm%, the white blood count 1200/cu.mm., with 86% lymphocytes and 12% neutrophiles. A bone marrow aspiration showed depression of all developing cellular elements. Over the next five days she received twelve units of whole blood, antibiotics, vitamins K and B_{12}, liver, folic acid and estrogens. On 1/16/66 she was transferred to the Minneapolis Veterans Administration Hospital because of difficulty in obtaining blood and platelets at the outside hospital.

Physical Examination

The blood pressure was 80/65, pulse 125 per minute, temperature 101° F. The patient was a well developed, slightly obese middle-aged white female who appeared pale and weak. There were multiple ecchymoses, particularly prominent in the right upper arm and right breast. The liver and spleen were not palpable. There was no lymphadenopathy. The vagina contained approximately 300 cc. of blood and clots, and active bleeding was observed from the cervical os. The uterus was twice normal size, quite firm and irregular.

Course

The patient was given multiple transfusions during her first hospital days to replace the blood loss and to return the blood pressure to normal levels. She was septic and remained so throughout her hospital course. Urine culture grew out E. coli and gamma streptococci. A blood culture on 1/21/66 produced a pseudomonas species and on 1/24/66, E. coli. The initial hemoglobin was 7.0 gm%, the white blood count 1500/cu.mm. with 24% neutrophiles, 72% lymphocytes, and the platelet count 25,000/cu.mm. The patient received a total of 41 units of blood and several courses of antibiotics. She also received prednisone, B_{12}, folic acid, nicotinic acid, multivitamins, thiamine and a course of phenylalanine. The white blood count fell to 240/cu.mm. on 1/29/66. Later that day, severe hemoptysis, combined with vaginal bleeding, respiratory distress and shock, led to death.

Autopsy examination showed a hypocellular bone marrow, pulmonary and bowel hemorrhage, gram-negative rods in the lungs and liver, and a postmortem blood culture grew out E. coli.

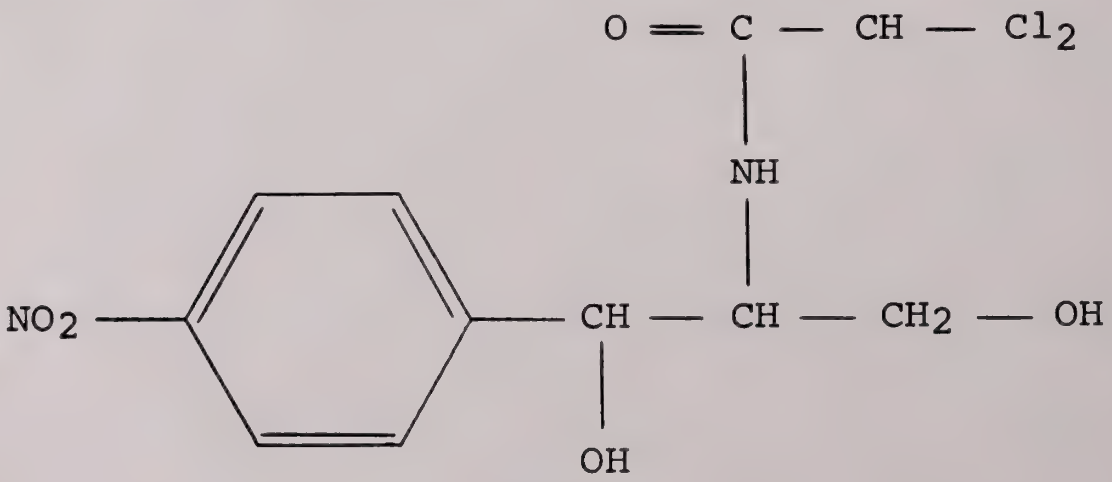
Case 2

A 65-year-old white male entered Minneapolis Veterans Hospital on 6/3/58 with symptoms and signs of intestinal obstruction. An operation had been performed at another hospital for lysis of adhesions and decompression of intestine obstruction five weeks prior to admission. On 6/18/58 a left hemicolectomy was performed and adenocarcinoma was found in the sigmoid colon. The regional nodes were not involved with tumor. Postoperatively the patient developed a pneumonia which was treated with penicillin 1,200,000 units and streptomycin 1.0 gm. b.i.d. from 6/20 to 6/27. On 6/27/58 chloromycetin 250 mg. q.i.d. was started and increased to 1.0 gm. q.i.d. on 6/30 through 7/9/58. The changes in white count, hemoglobin and platelet count are outlined in the Table.

The patient subsequently recovered from the surgery and postoperative pneumonia and was discharged. He returned to the Sioux Falls Veterans Hospital in 1960 with acute congestive heart failure. The hemoglobin was 13.5 gm% and the white blood count was 8750/cu.mm. with 80% neutrophiles and 12% lymphocytes. He was found to have metastatic adenocarcinoma and expired after a three-and-a-half month hospitalization. Autopsy examination showed a pale, fatty bone marrow which was not examined microscopically.

Clinical Picture

In patients developing aplastic anemia, as in Case 1, the onset is usually insidious with



Figure

gradually developing weakness and fatigue. Purpura or spontaneous bleeding from the nose, gastrointestinal or genitourinary tract may be the initial manifestation but most often comes after the onset of weakness and fatigue. Infections, while frequently the cause of death, are rarely the presenting manifestation.

Physical Findings

Physical examination usually shows a patient with a waxy pallor, often with ecchymoses, petechiae or spontaneous hemorrhage (epistaxis, rectal bleeding or menorrhagia). Late in the disease, ulcerations in the mouth or pharynx may appear, occasionally with a low-grade cellulitis in the neck. Splenomegaly is rarely present and when present is not of great magnitude. A markedly enlarged spleen is cause to doubt the diagnosis of drug-induced anemia and to suspect another cause, e.g., an "aleukemic" leukemia.[12]

Bone Marrow

Lesser damage to the marrow results in a wide spectrum of historical and physical findings. Case 2 showed an acute onset and apparently complete remission. A patient may have no clinical findings, the marrow damage being suspected only with examination of the peripheral blood for an unrelated condition. Historical and physical manifestations of similar nature, but less severe than those described for aplastic anemia, are observed in patients with milder forms of marrow damage.

Yunis and Bloomberg have divided chloramphenicol toxicity into two distinct types[13]: (1) a dose-dependent reversible type which appears concurrently with drug administration, and (2) the aplastic anemia variety which is not clearly dose-related and is usually fatal. It is implied that the reversible type represents the pharmacologic effects of chloramphenicol. Other distinguishing features include the following[13]:

TYPE I

Dose-dependent-reversible
Comes on during drug administration
Causes the erythropoietic lesion—no aplasia
Represents the pharmacologic effect
Median duration of therapy—20 days

TYPE II

Aplastic anemia—fatal
Delayed onset
No erythropoietic lesion seen
Represents idiosyncratic effect
Median duration of therapy—35 days

Bithell and Wintrobe[27] and Best[17] find that chloramphenicol toxicity is better described as a continuum of adverse effects. In Best's series of 408 cases reviewed from the AMA drug registry, there was significant overlap between Types I and II. Nine of 60 patients with

TABLE
Clinical Course of Patient 2

Date	WBC (leukocytes/cu. mm.)	Hgb. (grams/100 cc.)	Platelet Count (platelets/cc. mm.)
6/22	6,000	—	196,000
6/24	5,800	—	108,000
6/26	5,550	—	130,000
6/27			Chloramphenicol 1 gm/day
6/28	2,800	—	147,000
6/30	2,200	—	75,000 Chloramphenicol 4 gm/day
7/2	1,555	12.1	49,000
7/4	1,850	12.1	19,000
7/6	2,200	14.6	44,000
7/8	2,200	13.6	20,000
7/9	1,500	12.9	17,000 Chloramphenicol discontinued
7/12	1,550	14.0	21,000
7/14	1,700	13.8	18,000
7/15	3,850	14.0	23,000
7/17	5,500	14.6	42,000
7/21	9,050	14.4	205,000

Whole blood transfusions were given on July 1, 2, 3, 4, 10 and 14.

normocellular marrows had a two-week delay between the last dose of chloramphenicol and the appearance of toxicity. These data strongly suggest a continuum of marrow damage, and this view is supported by Bithell and Wintrobe.[27]

Metabolism

Chloramphenicol is completely absorbed from the gastrointestinal tract and reaches a serum concentration of 20-40 μg/ml. after a one-gram oral dose.[13] It is concentrated in the liver, lungs and kidneys. Detoxification occurs in the liver with formation of a glucuronide, 85% of a given dose being excreted in the urine within 24 hours. Only 10% of the excreted chloramphenicol is in an active form.[13] Thus, in uremic patients, the half-life of the metabolic products is increased, while patients with hepatic insufficiency have an increased half-life of the active form.[14] The bone marrow concentration parallels the plasma concentration. There is no evidence of sequestration of chloramphenicol in the bone marrow.[13]

Magnitude of the Problem

In assessing the magnitude of the problem with chloramphenicol toxicity, there are several avenues of approach. Complicating this assessment are inadequate reporting of toxic effects and frequent multiple drug ingestion in patients presenting with evidence of marrow injury.

Total Drug Distribution

The following figures from Parke-Davis Company* give the total number of grams of chloramphenicol distributed yearly from 1962 through 1967.

1962	26,427,000 gm.
1963	29,001,300 gm.
1964	28,382,900 gm.
1965	31,310,600 gm.
1966	32,834,500 gm.
1967	31,859,800 gm.

These figures reflect a yearly increase in distribution up to 1967, when Parke-Davis' patent rights expired and the drug was distributed by other companies. Inadequate reporting of toxic effects precludes precise correlation of toxic effects with total drug distribution.

Number of Adverse Reactions

The total number of chloramphenicol-associated blood dyscrasias reported to the AMA Registry on Blood Dyscrasias between 1953 and 1964 was 408, as reported by Best.[17] Forty cases formed the basis of an incomplete review of British experience.[18] Other reports include Yunis and Bloomberg's reported 94 cases of chloramphenicol-associated blood dyscrasias,[13] 21 of which were also included in Best's series.

Mortality-Morbidity

The Committee on Safety of Drugs of the British Medical Association reported 24 fatal cases of blood dyscrasias following chloramphenicol administration during 1965-66.[23] This comprised 80% of the reported fatalities from aplastic anemia during that time period. Unfortunately, not all of the patients listed in these reports were given the drug on the basis of the strict indications[17] called for in 1952[11] and repeatedly since that time.

Incidence

As stated above, the incidence of unfavorable hematological reactions to chloramphenicol is difficult to determine, as estimates vary widely. In 1952 Wilson[5] reported on 62 patients who had prolonged chloramphenicol administrations, one gram twice weekly, for bronchiectasis. Two developed aplastic anemia and one died: an incidence of one in 31 courses. Smick[24] derived an incidence of one in 60,000 four-gram "courses" of chloramphenicol. This was thought to be an underestimate of the rate of occurrence because of under-reporting of the toxic reactions. With the highly variable frequency of detecting and reporting adverse effects following chloramphenicol, it is difficult to properly assess the magnitude of the problem. Chloramphenicol remains the leading cause of drug-induced aplastic anemia in this country and Great Britain.[17,24-26] In addition, chloramphenicol has recently been implicated in the causation of leukemia.[19-21]

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*Kindly supplied by Dr. J E. Gajewski, Parke-Davis Co., Detroit.

Pathogenesis

The pathogenesis of chloramphenicol toxicity is not well understood at this time. Theories invoking the pharmacologic effect of the drug, auto-immunity and genetic susceptibility have all been proposed, but none proven.

Several features relevant to the pathogenesis have been observed. Chloramphenicol inhibits protein synthesis in rapidly proliferating tissues. Inhibition of protein synthesis was found to occur on the basis of inactivation of template ribonucleic acid.[28] Abnormal vacuoles in the proerythroblasts of the marrow can uniformly be induced by the administration of large doses of chloramphenicol.[31-34] Iron turnover is routinely inhibited by administration of large doses of chloramphenicol and precedes any morphologic evidence of marrow injury.[13,27,29,30] Scott et al. provide evidence that the abnormal iron metabolism is dose-related, with 6 gm/day routinely producing a decreased utilization of iron.[15] Bithell and Wintrobe suggest that the stem cell is the major site of injury, regardless of the mechanism of that injury.[27] Chromosomal breakage and vacuolization were observed following high doses of chloramphenicol.[39] Chromosomal injury could thus be the unifying mechanism for all the hematologic toxicity of chloramphenicol.

Long-Range Sequelae

It is the rare patient who survives chloramphenicol-induced aplastic anemia. Continued marrow hypoplasia with subsequent leukemia is illustrated in a case reported by Cohen and Creger.[19] Their patient was a young woman whose chloramphenicol-induced aplastic anemia was diagnosed in 1958 and who needed frequent blood transfusions until androgens were effective in raising the hemoglobin to acceptable levels. Seven years after the onset of marrow aplasia, the patient became resistant to androgens, developed acute myelogenous leukemia and died.

In a followup study, Fraumeni[20] reports a total of eight cases of leukemia following chloramphenicol-induced aplastic anemia. He reviewed the literature and found 13 cases of leukemia associated with prior chloramphenicol, two of them with aplastic anemia. In the eight patients who developed leukemia, three followed a sequence of drug—marrow aplasia with no evidence of leukemia—i.e., leukemia at least 18 months after the drug. This corresponds well to the sequence of events observed in irradiation-induced leukemias.

Additional cases of leukemia following chloramphenicol-induced marrow aplasia were described by Brauer and Dameshek.[21] Their three patients, like four of five of Fraumeni's, were all females over 35 who developed acute myelogenous leukemia. The time intervals to onset of leukemia were eight years, 14 months, and 18 months after the onset of marrow hypoplasia.

Acute myelogenous leukemia and chronic myelogenous leukemia are also seen following benzene or irradiation-induced marrow aplasia.

Since chloramphenicol-induced aplastic anemia is rare and usually fatal, it is not surprising that the late complications are just now being described. The fact that similar development of leukemia has followed other "induced" marrow aplasia, i.e., benzene, phenylbutazone and irradiation, should give added significance to the several reports of leukemia that have followed chloramphenicol-induced aplasia.

Treatment of Chloramphenicol Toxicity

Transfusions

Erythrocyte and leukocyte transfusions, platelet packs, antibiotics, isolation, androgens, and corticosteroids are useful in bone marrow aplasia but have largely failed to lower the overall mortality.

Phenylalanine

In 1965, Ingall and coworkers reported that phenylalanine reversed the bone marrow vacuole formation induced by chloramphenicol.[16]

Ward, however, was unable to reverse the *in-vitro* inhibition of hemoglobin synthesis by chloramphenicol with large quantities of phenylalanine.[35] Greenberg reported two adult patients in whom he was unable to reverse the chloramphenicol-induced abnormal ferrokinetics with phenylalanine.[36] Patient #1 also failed to respond to large doses of phenylalanine. It has been shown that phenylalanine *in vitro* does not effect suppression of phytohemagglutinin mitosis induced by chloramphenicol.[37] So it is doubtful that phenylalanine is the answer to chloramphenicol toxicity.

Bone Marrow Transplants

An attempt to treat hypoplastic anemias with marrow transplantation in a controlled study showed no significant improvement in survival for the twenty patients treated. In four of the twenty cases, marrow hypoplasia was attributed to chloramphenicol administration. One of the four showed a favorable response to marrow transplantation,[22] but this could not be substantiated subsequently.[12]

Cessation of Therapy

Monitoring the serum iron, iron-binding capacity and reticulocyte count is a means of detecting erythroid suppression in those patients receiving the antibiotic.[14,27] Even careful monitoring, however, is no guarantee of avoiding irreversible[13] marrow damage; therefore some authors[27,17] find it difficult to continue chloramphenicol in the face of manifest bone marrow injury and advocate cessation of therapy at the earliest sign of toxicity.

A dose of two grams of chloramphenicol per day has been proposed as a means of decreasing the incidence of dyscrasias.[15] However, the development of aplastic anemia has not been shown to be dose-dependent, so that aplasia cannot with certainty be avoided with any dose schedule.[27]

Hepatic and renal insufficiency which modify the conjugation and excretion of chloramphenicol should be considered as relative contraindications to its use.[14,27] The frequency of marrow aplasia is increased with intermittent therapy; therefore intermittent administration of the drug is to be avoided.[13,17,27]

Prognosis

The following factors have been found to favorably influence prognosis[13,17]:

1. Fewer cell types depressed in both the peripheral blood and in the bone marrow;
2. A shorter delay in onset of marrow toxicity;
3. A larger daily dose of chloramphenicol (rapid induction of marrow suppression is more often reversible);
4. Occurrence in persons of the negro race;
5. Fetal hemoglobin above 400 mg%.

The mortality rate is quite high for the delayed-onset, hypoplastic group. In Yunis and Bloomberg's group of 94, 43 patients showed delayed onset, and 38 of these died.[13] In this same series, 49 patients had the onset of marrow suppression during chloramphenicol, and 11 of these died (Figure 3).

Figures from the AMA registry show that 108 of 279 patients with chloramphenicol-associated marrow toxicity had died, 96 had recovered, and 75 were alive with sequelae.[17] There were 31 deaths among 40 cases reported by Sharp.[18]

Bloom and Diamond[38] report 11 children with chloramphenicol-induced marrow aplasia, nine of whom died. Eight of eight with a fetal hemoglobin value below 400 mg% died, whereas only one of three with a value above 400 mg% died.

Prevention

The most effective means of avoiding toxicity from chloramphenicol lies in prevention. Most of the 408 patients in Best's review received chloramphenicol in the recommended dose and duration. However, it was alarming to note the fatal cases of aplasia which resulted from treatment of the common cold, acne, and viral and bacterial respiratory infections with chloramphenicol. A decrease in the unwarranted use of chloramphenicol is the chief means of prevention now available to physicians.[13,17,27]

Summary

Two diverse cases serve to emphasize the variability of the hematologic complications of chloramphenicol toxicity. Difficulties in assessing the magnitude of the problem are largely related to lack of complete reporting of cases. A review of pathogenetic factors fails to completely explain the genesis of chloramphenicol-associated marrow injury. Leukemia has recently been reported as a late complication. Treatment of the aplastic anemia is quite unsatisfactory. Another case (Case 1) unresponsive to phenylalanine is reported. The prognosis for a patient with both pancytopenia and hypocellular marrow is almost nil. Factors influencing prognosis are reviewed. A decreased use of chloramphenicol remains the chief means of preventing its dangerous hematologic toxicity.

References may be secured from the author or the reprints.

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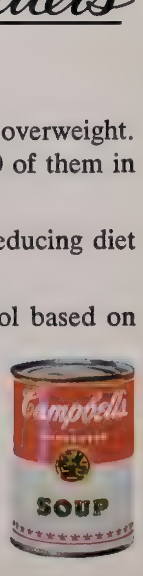

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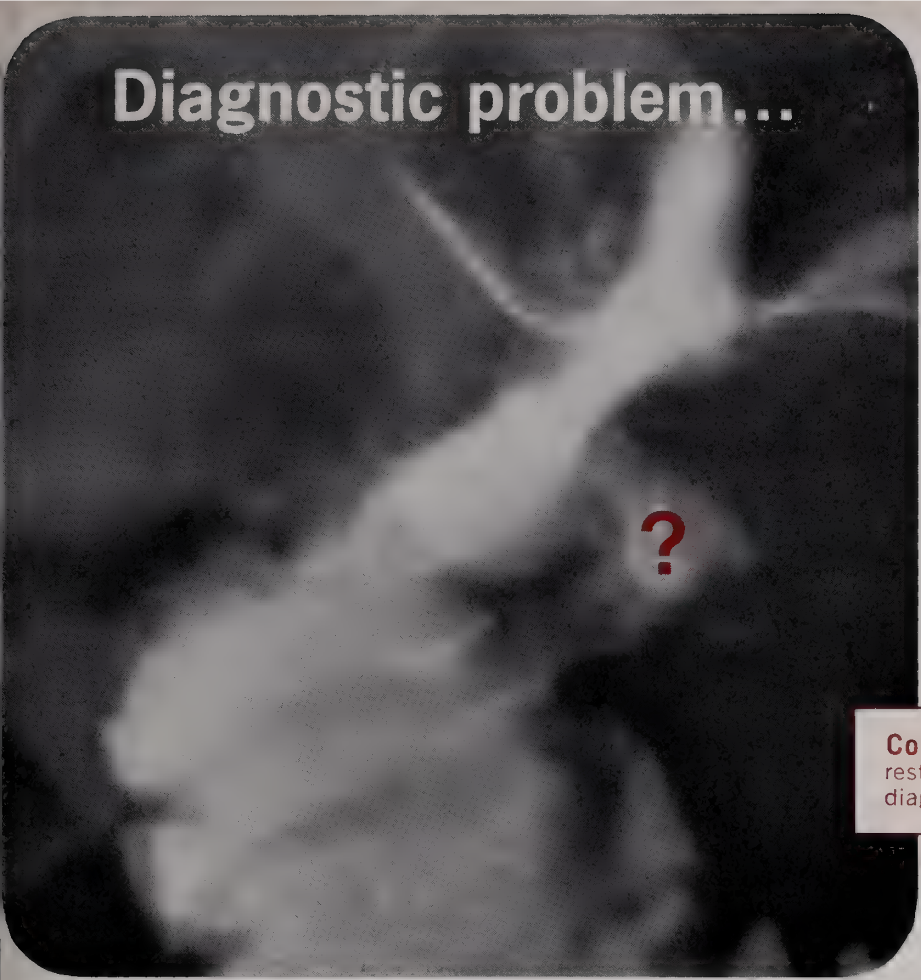
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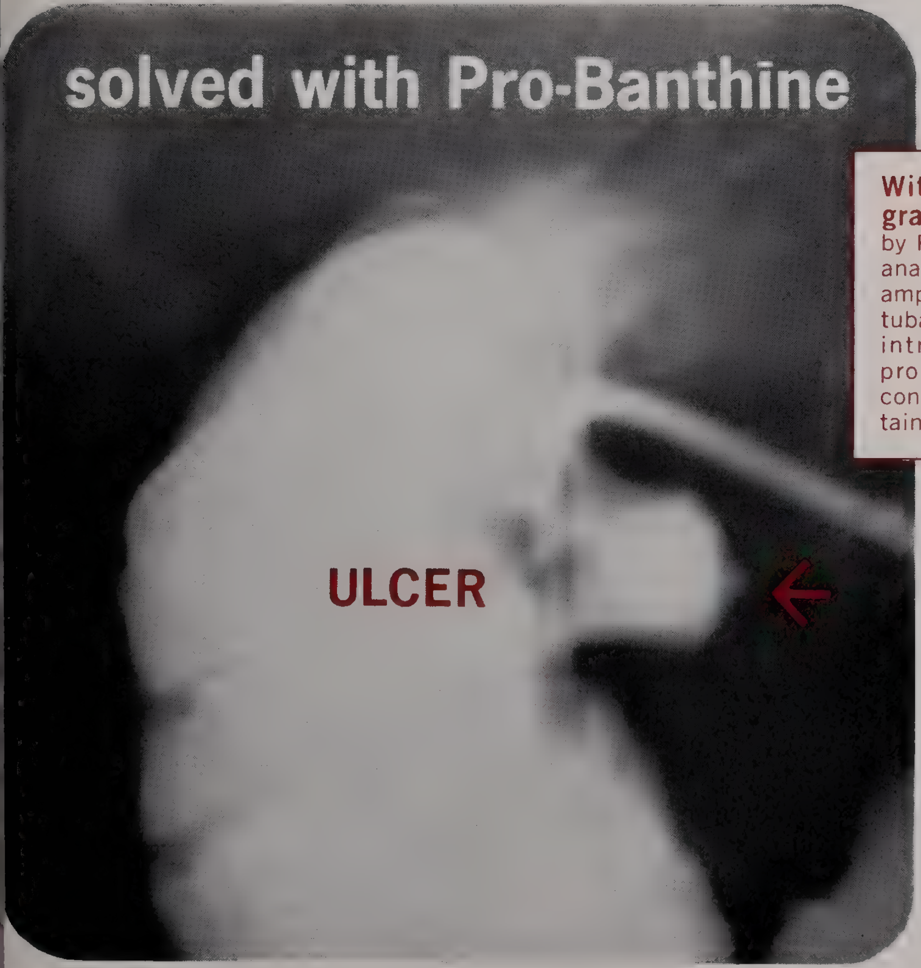
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Editorials

Malignant Tumors in Children

DURING THE PAST thirty years, the prevention and treatment of many bacterial and viral diseases have diminished their role as a cause of death in children. Similar improvements have not been as striking in the cure of malignancy; therefore the importance of neoplasms has become relatively greater. Malignant tumors now rank second only to accidents as a cause of death in the age group from one to fifteen years.

In this issue,* Doctors Mahour and Lynn present a very interesting review of the remarkable variety of tumors encountered during the pediatric span. The importance of teamwork on the part of the clinician, radiologist, surgeon and pathologist is stressed in the diagnosis of neoplasms. Each physician involved in the care of children should maintain a high index of suspicion regarding tumors and in seeking the cause of symptoms not readily explained.

Progress in pediatric oncology† has been hampered by many factors, including the obvious difficulty in conducting controlled series to evaluate different methods of treatment. In addition, the sporadic distribution of affected patients slows the evaluation of new treatment techniques until a significant series accumulates. A most encouraging trend to combat these problems is the national and regional cooperation of physicians interested in childhood malignancy, combining their data in controlled studies and sharing the information derived.

Just as teamwork was stressed in the initial diagnosis of neoplasms, it is vitally important in the subsequent management of the patient. Close collaboration of the attending team, including the child's regular physician, will minimize delays, concentrate the available knowledge and avoid confusion for the family.

There is ample reward for the extra effort in the gratification of seeing a child cured and in the increased skill and knowledge acquired by the team. If the disease should progress toward a fatal outcome, we must remember that "incurable" does not mean "untreatable;" and the team must continue to assist in a genuine effort to sustain the comfort and morale of the young patient and his family.

Bernard J. Spencer, M.D.
Minneapolis, Minnesota

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*See page 1679.
†See Test Your Word Score Page 1637.

Reference

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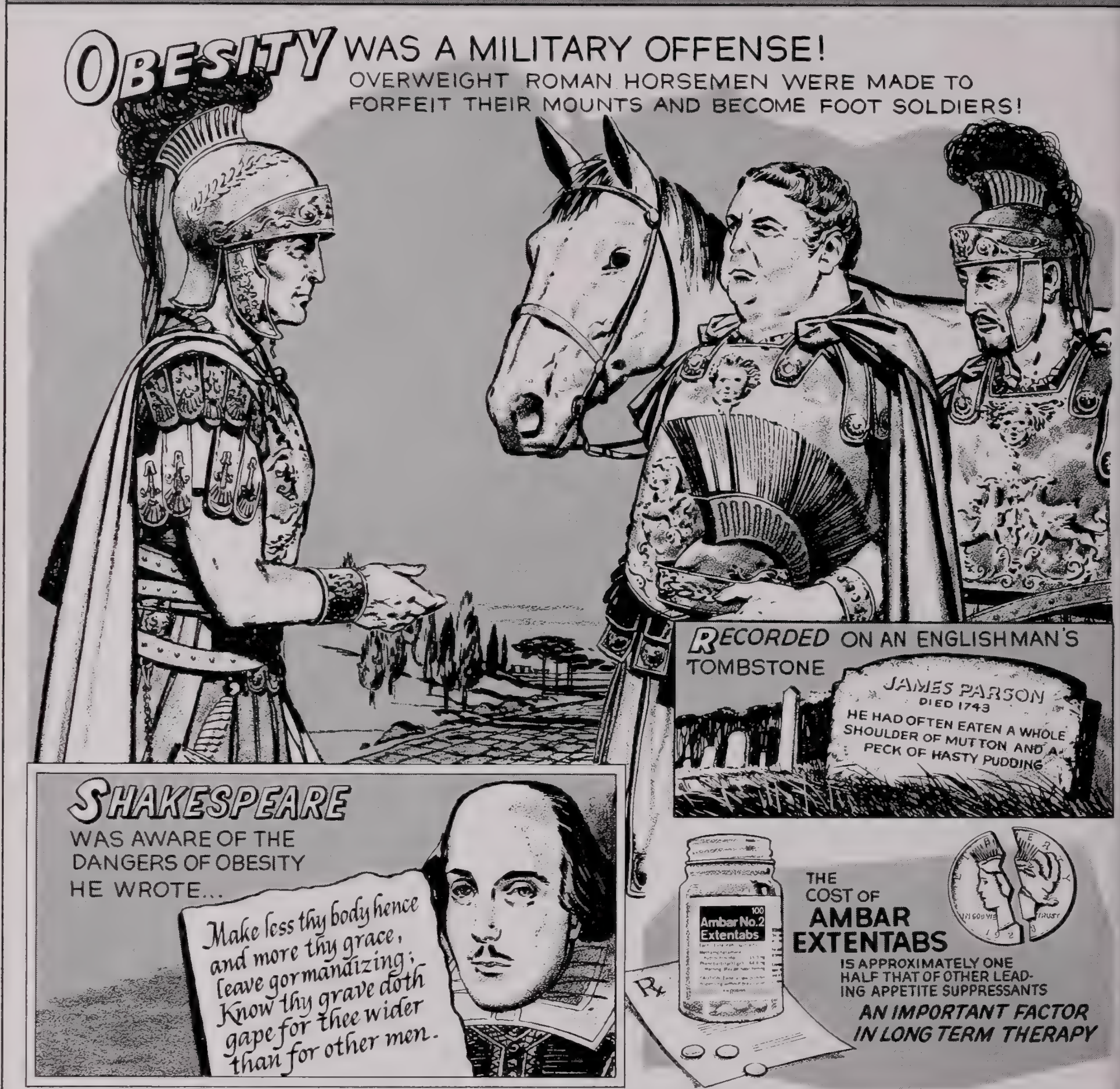
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Electronic Pacemakers

The development of implantable artificial electronic pacemakers as reviewed by Bonnabeau and Lillehei[1] has been one of the major medical advances of this century. Patients with complete heart block who ordinarily would have had a life expectancy of one year or less may now be returned to useful life, with the Damocles sword of Adam-Stokes attacks effectively removed.

The combination of implantable battery unit and bipolar intracardiac catheter has obviated the need for thoracotomy and made the procedure a benign one that can be performed under local anesthesia, even with patients of advanced age who are poor surgical risks. The development of a demand type pacemaker which can be inhibited if normal sinus rhythm returns has almost entirely eliminated the problem of pacemaker-induced arrhythmias.

A difficult problem is posed by the patient who has a history of syncopal episodes with slow pulse but who, at the time of admission to the hospital, is found to have normal sinus rhythm. The patient should be monitored and, if episodes of transient AV block are demonstrated, a demand pacemaker should be inserted. A helpful clue in this situation is the presence of right bundle branch block with marked left axis deviation. This suggests partial bilateral bundle branch block.[2]

Another development in the use of pacemakers has been the treatment of arrhythmias. Patients with recurrent ventricular tachycardia refractory to medical management have responded to pacemaker treatment with the rate of the artificial pacemaker set fast enough to inhibit the ectopic focus.[3]

After a decade of use the implantable electronic pacemaker is here to stay.

David Berman, M.D.
Minneapolis, Minnesota

References

1. Bonnabeau, R. C., Jr. and Lillehei, C. W.: Development of Controlled Cardiac Pacemaking. Minnesota Med 52:871, 1969.
2. Lasser, R. P., Haft, J. I., Friedberg, C. K.: Relationship of Right Bundle Branch Block and Marked Left Axis Deviation (With Left Parietal or Peri-infarction Block) to Complete Heart Block and Syncope. Circulation 37:429, 1968.
3. McCallister, B. D., McGoon, D. C., and Connally, D. C.: Paroxysmal Ventricular Tachycardia and Fibrillation Without Complete Heart Block. Amer J Cardiol 18:898, 1966.

Post-Intubation Granuloma of the Larynx

Post-intubation granuloma, described in Minnesota Medicine,* although not a common complication of general endotracheal anesthesia, must be suspected in a patient with "choking" and hoarseness following intubation. The site of the lesion in the posterior or "breathing" area of the laryngeal introitus explains why breathlessness or choking may precede hoarseness.

Anesthesiologists, of course, are aware of this problem; but their meticulous fitting and placement of endotracheal tubes may be offset by enthusiastic passive head movements and other head positions required in certain surgical situations. Recognition of the etiologic factors by all operating-room personnel should be expected to keep this a relatively rare complication of endotracheal anesthesia.

Melvin E. Sigel, M.D.
Minneapolis, Minnesota

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*Schlorf, R. A. and Duvall, A. J. III: Post-Intubation Granuloma of the Larynx. Minnesota Med. 52:717, 1969.

"All Interns are Alike"

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Corrective Surgery in Elderly Patients
A Dilemma

As surgical skills and supportive techniques become honed to a sharp edge of perfection, those patients whose tolerance for a major intervention or stress is marginal may often be offered corrective surgery—even open heart surgery. Age alone is not to be regarded as an absolute contraindication to a given operation; rather it merely enters into the balance of pros and cons that determine the advisability or inadvisability of a procedure. In the last analysis, this balance involves the odds for death or disability if operation is performed, as opposed to nonintervention. The octogenarians operated on by Kiser and associates,* as reported in this journal, had less to gain from operation because life expectancy at their age was shorter; thus the cost and pain of operation would be rewarded by a much diminished period of benefit resulting therefrom. Also, the risk and morbidity for patients in their seventies, everything else being equal, must surely be higher. But even these less favorable indications for operation may not be of sufficient importance to militate against the scalpel, because longevity and the pleasure of living may be so improbable otherwise that operation becomes an attractive alternative, as for these patients of Kiser, Peterson, and Johnson, and for several of our own patients.

It might be of interest, and indeed is now becoming something of a necessity, to pursue this line of reasoning to a more radical conclusion—or dilemma(?). Suppose that an aged patient has a life-threatening malfunction, for which a corrective or highly palliative and safe therapeutic intervention is available. According to the previous reasoning, this therapy, or even surgery, is justified and indicated. I have in mind, as an example, the development of heart block, with its attendant syncope, cardiac failure, or sudden death, and the availability of pacemakers placed transvenously and under local anesthesia at very low risk but considerable expense. But now suppose the patient, in addition to old age and heart block, has senility, loss of memory, painful arthritic contractures, personality derangement and paranoia, and failing vision. Neither the patient, his relatives, society, nor the doctor can muster enthusiasm for the insertion of a pacemaker to prolong his deteriorating existence. But exactly where is the line to be drawn? And when is that line crossed? Who is to assume the responsibility of decision?

These are the same unanswered questions that have made merciful euthanasia unacceptable. However, the advances of medical science prevent further deferment of this issue. Indeed, euthanasia by the withholding of supportive therapy is now generally considered acceptable for certain terminal patients with incurable disease, such as cancer. Senility also is incurable, and its ravages are extensive. Most physicians and surgeons already practice a modified form of euthanasia by withholding treatment from the most pitiful of the aged and infirm.

Hopefully, the perfection of artificial hearts and similar modalities will not precede the formulation of ethical guidelines for the physician to follow in his practice of modified euthanasia. But if pacemakers, artificial valves, and even artificial hearts can be withheld so as not to prolong a patient's incurable senility, why not the same for antibiotics, vitamins, or even nutriment. And if we are to manipulate the phenomenon of death by withholding these available means of prolonging life in order that death may arrive sooner through infection, inanition, or congestive heart failure, why should we tolerate even these extended and miserable types of death? Once senility has irreversibly destroyed the personality and disrupted meaningful contact with reality, should we not be consistent in our mercy and *invite* death's painless and welcome peace?

Dwight C. McGoon, M.D.
Rochester, Minnesota

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*Kiser, J. C., Peterson, T. A., and Johnson, F. E.: Open Heart Surgery in Elderly Patients. Minnesota Med 52:231, 1969.

Prejudice, which sees what it pleases, cannot see what is plain.—DeBere.

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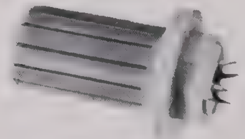

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Vaginal Hysterectomy*

VAGINAL HYSTERECTOMY is one of the oldest gynecologic operations known. The excessive morbidity and mortality of operative procedures performed prior to this century, when coupled with the inherent complications of vaginal surgery itself, caused vaginal hysterectomy to fall into disrepute.

With the advent of improved anesthesia, transfusions, antibiotics, and postoperative care of medical complications, vaginal hysterectomy has rightfully gained a respectable role in the armamentarium of the pelvic surgeon. Mayo, Heaney, Counsellor, Pratt, and others have demonstrated that the procedure can be done with a low rate of mortality, diminished operative time, shortened hospitalization, and a minimum of significant complications. However, the improvements themselves are not indications for a major operative procedure when medical therapy, with no risk, may be as effective or when a minor procedure such as curettage may suffice.

In the present-day practice of gynecologic surgery, approximately half of the hysterectomies performed are carried out through the vagina. This proportion has been maintained during the past 10 to 15 years when appropriate indications are observed.

Several factors concerning the indications for vaginal hysterectomy should be stressed. The data from the large series of Tasche demonstrate once more that the two main indications for vaginal hysterectomy are abnormal vaginal bleeding and symptomatic pelvic relaxation. Other symptoms as well as findings on pelvic examination may give a summation effect, indicating vaginal hysterectomy, with or without repair, when no one symptom or finding in itself would be an indication for a major operative procedure.

Although vaginal bleeding is a common indication for hysterectomy, the possibility of malignancy *must* be ruled out prior to the performance of a definitive procedure that may not be the treatment of choice for a malignant condition. A negative smear does not rule out the presence of malignancy in the female pelvis and means only that malignant cells were not seen. If a cervical abnormality is noted, a biopsy specimen should be taken; if there is abnormal bleeding, a definitive diagnosis must be made by means of curettage; and if there is discharge or any other findings indicative of malignancy, the possibility of malignancy also must be ruled out prior to the performance of a simple vaginal hysterectomy.

In invasive carcinoma of the cervix, vaginal hysterectomy is inadequate when performed alone. The five-year survival rate for invasive carcinoma of the cervix treated by simple hysterectomy is 14%, as compared to the 85% anticipated with proper treatment. Similarly, in carcinoma of the endometrium, bilateral salpingo-oophorectomy probably should be done in addition to the hysterectomy, as a simple hysterectomy may not be adequate. In carcinoma of the endometrium, vaginal hysterectomy with bilateral salpingo-oophorectomy gives excellent results, comparable to those with the abdominal approach. However, the abdominal approach is preferable because it allows for more adequate exploration so that extension of the disease process may be treated properly; it also decreases the risk of adnexectomy.

Any organic disease that will cause persistent vaginal bleeding may be properly treated by means of vaginal hysterectomy. As a major operation, vaginal hysterectomy, in the absence of organic disease, should be carried out *only* when the bleeding is recurrent or has not responded to previous curettage or hormone therapy.

Symptomatic pelvic relaxation is now the primary indication for vaginal hysterectomy. Although vaginal hysterectomy is presently the treatment of choice, the operation is incomplete without repair of other damaged tissues, cystocele, urethrocele, rectocele, and enterocele. Symptoms of pelvic pressure, bearing down, falling out or bulging of tissue, and stress incontinence may be expected to be ameliorated by vaginal hysterectomy and repair. Urgency incontinence is often noted in conjunction with these symptoms; however, the urgency is related to irritation of the bladder and will not be ameliorated necessarily by any surgical pro-

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*Tasche, L. W.: 1700 Vaginal Hysterectomies in a General Surgical Practice. Minnesota Med 51:1705, 1968.

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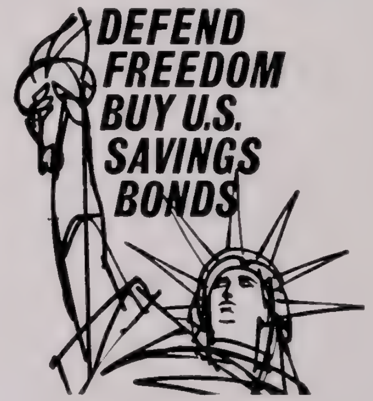

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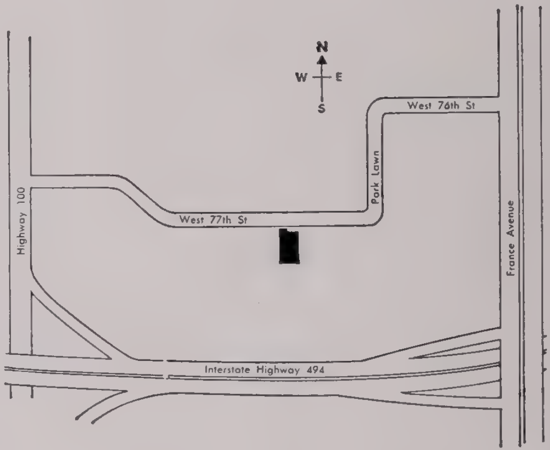

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cedure, whereas correction of the urethrovesical angle by means of plication and cystocele repair is designed to correct stress incontinence. Only if the urgency incontinence from the irritated bladder is secondary to its prolapse is the urgency incontinence likely to be improved by vaginal repair.

Just as vaginal repair is an integral part of the hysterectomy performed for symptomatic pelvic relaxation, the converse is equally true. Only in the most extenuating circumstances is vaginal repair indicated without performance of vaginal hysterectomy. Technically, the damaged tissues can be better repaired with the uterus removed. Subsequently, the uterus will not adversely affect the repaired region, either by pregnancy or tumor formation. Because the uterus is the site of about 12% of malignant lesions in the female, it should be removed at major pelvic surgery unless there is a decision to maintain the function of childbearing.

Inasmuch as the chance for success is best in the first operation performed for pelvic relaxation, the procedure must be done completely at the initial attempt. The single most important measure in preventing recurrence of prolapse is the obliteration of the cul-de-sac and repair of the enterocele, whether obvious or incipient. Careful attention to surgical technique during the operative procedure will decrease the morbidity. Previous pelvic surgery and pathologic conditions alert the surgeon to expect complications during vaginal hysterectomy. The procedure should be performed when it is considered to be the proper operation for the patient's condition and when it carries the least risk to the health and wellbeing of the patient herself. Tasche's article demonstrates again that an experienced surgeon may safely perform vaginal hysterectomy with a minimum of risk and morbidity to the patient. In addition to the surgical technique, the appropriate indications and contraindications must be observed to provide good results.

Tiffany J. Williams, M.D.
Rochester, Minnesota

Test Your Word Score

Nihilistic—*characterized by a feeling that conditions are so bad that destruction or denial is desirable* (page 1599).

Dichotomy—*division into two contradictory parts* (page 1601).

Anlage—*tendency, proclivity* (page 1602).

Thrombocytopenia—*decrease of platelet count* (page 1605).

Polycythemic—*having an increased number of red cells* (page 1610).

Monoclonal gammopathies—*one group of cells producing abnormal globulins* (page 1615).

Oncology—*the study of tumors* (page 1629).

Panniculitis—*inflammation of deeper tissue of the skin* (page 1668).

Astereognosis—*loss of power to recognize objects or to appreciate their form by touching them* (page 1700).

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Precautions: In suspected staphylococcal infections, perform proper laboratory studies including sensitivity tests. If overgrowth of nonsusceptible organisms occurs (constant observation is essential), discontinue penicillin and take appropriate measures. Whenever allergic reactions occur, withdraw penicillin unless condition being treated is considered life threatening and amenable only to penicillin. Penicillin may delay or prevent appearance of primary syphilitic lesions. Gonorrhea patients suspected of concurrent syphilis should be tested serologically for at least 3 months. When lesions of primary syphilis are suspected, dark-field examination should precede use of penicillin. Treat beta-hemolytic streptococcal infections with full therapeutic dosage for at least 10 days to prevent rheumatic fever or glomerulonephritis. In staphylococcal infections, perform surgery as indicated.
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The Editor's Soliloquy

Canned Consultation

THROUGH NORTHLAND REGIONAL the federal government has provided consultation for the doctor "in the far corner of the state" who lacks the availability of highly trained specialists in the adjoining office or down the street. All he has to do is lift the receiver and dial the number: 1-800-356-8103. A mechanical voice speaks out and gives him an official consultation.—Easy, wasn't it? The consultation didn't cost a dime; even the phone call was free.

The calling physician has no opportunity either to greet the disembodied voice with a cheery "Hi" or to conclude the non-stop interview with a warm "Thank you" or "Goodbye." He has no chance to establish professional rapport with another gentleman through the subtle reciprocity of voice inflections conveying understanding, assurance and confidence. There is no possibility of interrupting the steady flow of words with a polite query for clarification: "What was that again?" or to inject a responsive remark: "That sounds encouraging; I'm glad you mentioned that!" There is no intimately mutual and profitable exchange: just a continuous monologue over the wire, calculated to leave the frustrated caller feeling nullified.

Does it sound as if I'm being facetious? You're right, I am! But if, under my jocosity, you, the reader, fail to detect a deep concern, then you don't know your Editor. In this state of ours, where medicine is practiced on the highest grade, the federal government is spending one and a quarter million dollars to implement this and other innovations for the postulated "improvement" of the physician, with not one penny of this money allocated to the care of the "neglected patient."

Does this not seem like a shocking reversion of priorities: another of those confounding paradoxes the perversely meshed gears of our complex age have been producing so abundantly of late? It is!

Can you imagine any physician, any specialist, who would not willingly provide free telephone consultation at any time, day or night, to any colleague who needed and requested it? Why not call up Northland Regional and ask them to spend some of that one and a quarter million dollars to pay for the phone calls? We'll give the consultations free, and they won't be canned! Try it!

Carl O. Rice, M.D.

Old Doc Hess says: Expounding too contentiously about the infinite advantage of one minutia over another begins to assume the proportions of a cult—not a science. COR

The excesses of our youth are drafts upon our old age, payable with interest about thirty years after date.—Colton

(President's Letter continued from page 1583)

and the training-grant facilities have improved this opportunity.

The National Program for Dermatology recently formulated by the American Academy of Dermatology outlines programs for various types of professional and nonprofessional personnel, facilities for the care of diseases of the skin, types of required equipment, and specific projects designed to solve the major public and personal health problems related to the skin. The guide thus provided demonstrates and can help answer most of the needs of the American public in respect to dermatology. Three members of the 15-man National Council for Dermatology were trained in Minnesota.

In Minnesota we are in the happy position of being among the leaders both in providing care and in providing professional personnel in dermatology. The progress we have made and our position of leadership throughout the country must not dull our capacity for self-assessment, however. The University of Minnesota, for instance, does not have a full-time professor of dermatology. It is well accepted that three full-time faculty positions are the minimum necessary for the satisfactory conduct of a department. The level of financial support provided by the legislature for our state medical school is far below that given to most other state-supported schools in the United States. The University of Minnesota Medical School receives a third or less of its budget from the State of Minnesota. It is a tribute to the personnel of the University of Minnesota that they have maintained their excellent standard of medical care, teaching and research in the face of the deprivations and restrictions with which they must deal. The evolution of a second medical school in this state would carry with it the promise of full-time faculty positions so that new departments, and not only departments of dermatology, could develop from the beginning.

R. K. Winkelmann, M.D.*
President
Minnesota Dermatologic Society

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*Professor of Dermatology, Mayo Graduate School of Medicine.

Reference

Baer, R. L. (ed.): National Program for Dermatology. Published by the American Academy of Dermatology, 208 pp., May 1969.

Emerging Patterns of Medical Care and Practice

The central plot of this story is, in a sense, the central plot of all social history —man's struggle to rearrange his social organization and institutions, to keep pace with his accumulating knowledge, changing needs and altered environment. As in all phases of human enterprise, realistic available choices are limited, but they are not absent. Freedom to avoid the basic fact of change does not exist—either biologically or socially—but the character and adequacy of the adjustment to change is, in varying limits, subject to human decision. It is, of course, possible for a society or a group to attempt to resist adjustments altogether—either actively or by inertia—but the price is to be run over.*

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*H. M. Somers and A. R. Somers in Richard Magraw: Ferment in Medicine, 1966.

Man of Action

Musician Fats Waller says he became acquainted with a set of twin brothers. One was a minister and the other a doctor. He met the medical brother on the street one day and said, "I wish to compliment you on your fine sermon last Sunday, Doctor."

The twin shook his head and replied, "I'm sorry Waller, but I'm not the doctor who preaches—I'm the one who practices."*

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*Maxwell Droke: The Speaker's Handbook of Humor.

Curbstone Consultation

QUESTION: What is the currently recommended treatment of superior sulcus or Pancoast tumors?

ANSWER: Superior sulcus tumors, first described by Pancoast, are peripheral bronchogenic carcinomas of the lung which invade the apical chest wall and produce a typical clinical picture of shoulder and arm pain, Horner's syndrome, and usually ulnar nerve paresthesia due to invasion of the brachial plexus. Rarely, other conditions such as tuberculosis or Hodgkin's disease may produce this picture. These tumors tend to progress slowly, locally, and to metastasize late.

The preferred treatment includes preoperative radiotherapy using a subcancerocidal dose of 3000 rads given in ten treatments over twelve days, followed in four weeks by en-bloc resection of the upper two to three ribs, apical segment or, generally, the upper lobe and if necessary any involved portion of the brachial plexus. The subclavian vessels can usually be preserved although resection of the artery with graft replacement has been carried out. Surgery is performed, however, only in the absence of metastatic disease as determined just prior to the scheduled date of operation. Occasionally, patients have shown the development of metastases during the four-week period following radiotherapy. The subcancerocidal radiodosage used tends to sterilize the periphery of the tumor and yet tends not to increase the operative complications as seen with higher dosages. Some workers advise against biopsy of the lesion, especially by thoracotomy, before initiating the radiotherapy, because of interference with the radioresponsiveness of the tumor due to the surgical reaction as well as an increased risk of dissemination of the tumor from this manipulation. These workers are willing to proceed with therapy on the basis of the typical clinical syndrome produced by these lesions and have found no consequence from the radiotherapy in the few cases where the cause of the syndrome was some other condition.

Needle biopsy of the lesion through the supraclavicular fossa may provide a pre-treatment diagnosis without as much interference with radioresponsiveness. With this combined therapy the survival rate has been significantly improved: an approximately 35 percent three-year survival; whereas formerly there were rarely any survivors at this time period following radiotherapy alone, surgery alone, or surgery plus postoperative radiotherapy.

Raymond G. Armstrong, M.D.
Lackland Air Force Base, Texas

References may be secured from the author.

Meetings and Announcements

American Medical Writers Association

The North Central Chapter of the American Medical Writers Association meeting November 1, 1969, 1:00 P.M., Judd Hall, Mayo Clinic, Rochester, Minnesota. Social hour and dinner, New Sheraton, Rochester, 7:30 P.M. All doctors interested in medical writing are welcome, wives included.

University of Minnesota

Medical Oncology Today

The University of Minnesota will conduct a course on October 8-11, for the American College of Physicians dealing with the application of Medical Oncology to clinical practice. The course will be aimed particularly at the practicing internist.

Automotive Medicine

The University of Minnesota will present a program dealing with medical aspects of automobile and other transportation injuries on October 16-18, 1969. This program is co-sponsored by the American Association for Automotive Medicine and should be of interest to all physicians dealing with trauma and other medical conditions resulting from transportation injuries.

Diabetes

The University of Minnesota will present a course in Diabetes Management and Control on October 22-24, 1969. The course will be co-sponsored by the Twin Cities Diabetes Association.

Urologic Radiology

The University of Minnesota will present a course in Urologic Radiology on October 27-31, 1969. For further information on all of the above courses contact: Lee D. Stauffer, College of Medical Sciences, Box 193 Mayo Building, University of Minnesota, Minneapolis, 55455.

Mayo Clinic Clinical Reviews

A program of lectures and discussions on problems of general interest in medicine and surgery will be held at the Mayo Clinic and Mayo Foundation, Rochester, Minnesota. Identical sessions are offered on November 3, 4, 5, 1969 and November 10, 11, 12, 1969.

This program is acceptable for credit by the American Academy of General Practice and the College of Family Physicians of Canada. The registration fee for this program is $20.

The number of physicians who can be accommodated is necessarily limited. For this reason identical programs will be offered two successive weeks. The program will be presented first on November 3, 4, 5, and repeated on November 10, 11, 12. Those wishing to attend should communicate with M. G. Brataas, Mayo Clinic, Rochester, Minnesota 55901, indicating which session they would prefer to attend.

The Viewing Box

Weakness and Backache

A 32-YEAR-OLD white female was admitted to the hospital complaining of weakness and backache on the left side. A routine urinalysis showed 10 to 15 red blood cells per high-power field; a repeat urinalysis three weeks later showed 60 to 75 red blood cells per high-power field. A chest x-ray showed a coin lesion in the right lower lobe. An intravenous pyelogram was done and suggested a deformity of the lower calyx of the left kidney.

Because of the history and laboratory findings a renal arteriogram was performed using 60% Hypaque (Figure 1). A tumor blush was suggested involving the lower pole of the left kidney (Figures 1 and 2). The findings, however, were inconclusive; so 12.5 micrograms of epinephrine were injected intra-arterially, with the catheter directed into the left renal artery. Sixty seconds later 8 cc. of 60% Hypaque were again injected through the catheter. Serial x-rays were taken which demonstrated an absence of small arterial branches in the left kidney, but a persistence of the fine arterial network distributed in the region of the lower pole (Figure 3).

What is your diagnosis? (See next page.)

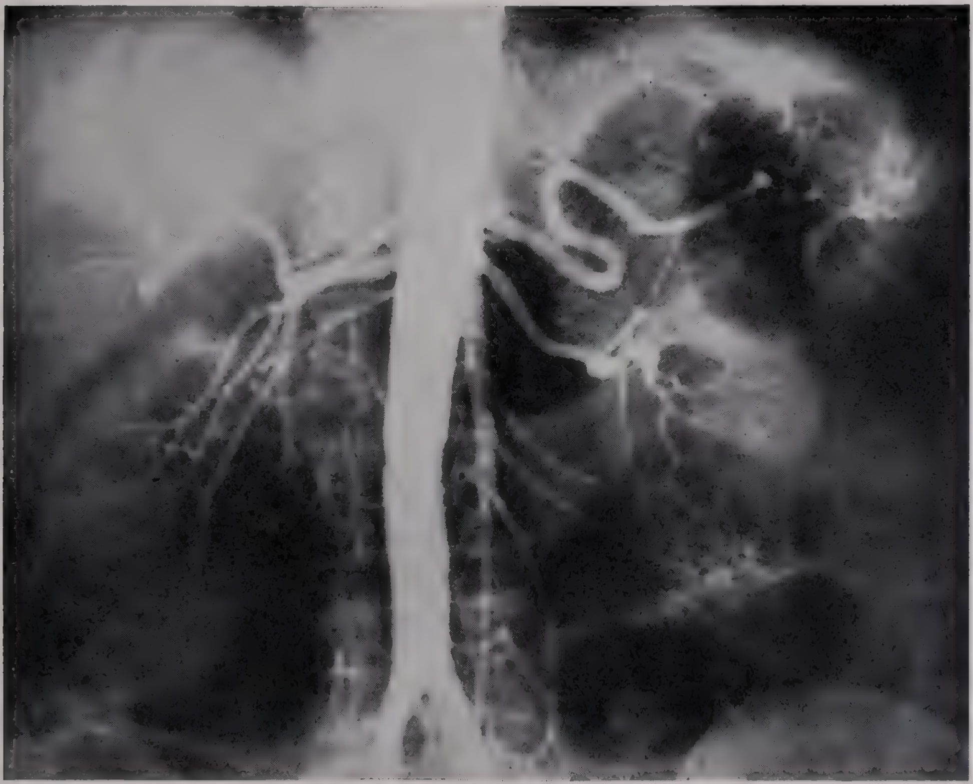

Figure 1

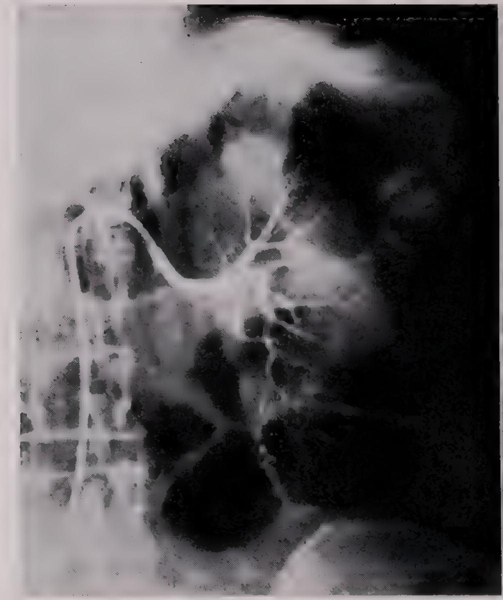

Figure 2

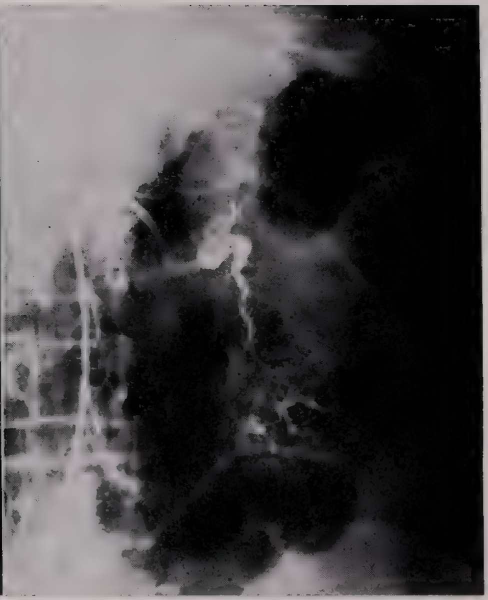

Figure 3

Diagnosis: Renal carcinoma of left kidney.

The patient underwent a left nephrectomy and a clear cell renal carcinoma of the lower pole of the left kidney was found. She made an uneventful recovery from her surgery with disappearance of her preoperative symptoms and hematuria. Four months postoperatively her chest lesion has shown no change, and it is planned to follow her at monthly intervals. A certain number of solitary pulmonary metastatic nodules from renal cell carcinoma will regress, or even disappear, after removal of the primary tumor. If the presumed metastatic pulmonary lesion does not regress or increases in size, excision will be advised.

The demonstration of a tumor blush by renal arteriography is convincing evidence of renal carcinoma. Abrams[1] devised a method for improving diagnostic accuracy in deciding whether or not a tumor blush exists by injecting epinephrine into the renal artery of the kidney in question. With this technique the small arterial branches supplying the normal renal parenchyma become obliterated, whereas the arterial networks supplying the carcinoma are unaffected. This serves to accentuate the radiographic appearance of the tumor blush on injection of contrast media by more blood being shunted through the arterial channels supplying the tumor as contrasted with those supplying the normal parts of the kidney.

The phenomenon of vasoconstriction of normal small renal arterial vessels by epinephrine while leaving unaffected the arterial supply to the neoplasm has also found application in treating renal tumors with cancer chemotherapeutic agents. By injecting epinephrine into the renal artery prior to injection of the cancer chemotherapeutic drug a situation results in which the blood supply is diverted from normal kidney to neoplasm. This results in a heavier concentration of the drug being delivered directly into the tumor mass.

Rafael S. Misa, M.D.*
Montgomery, Alabama

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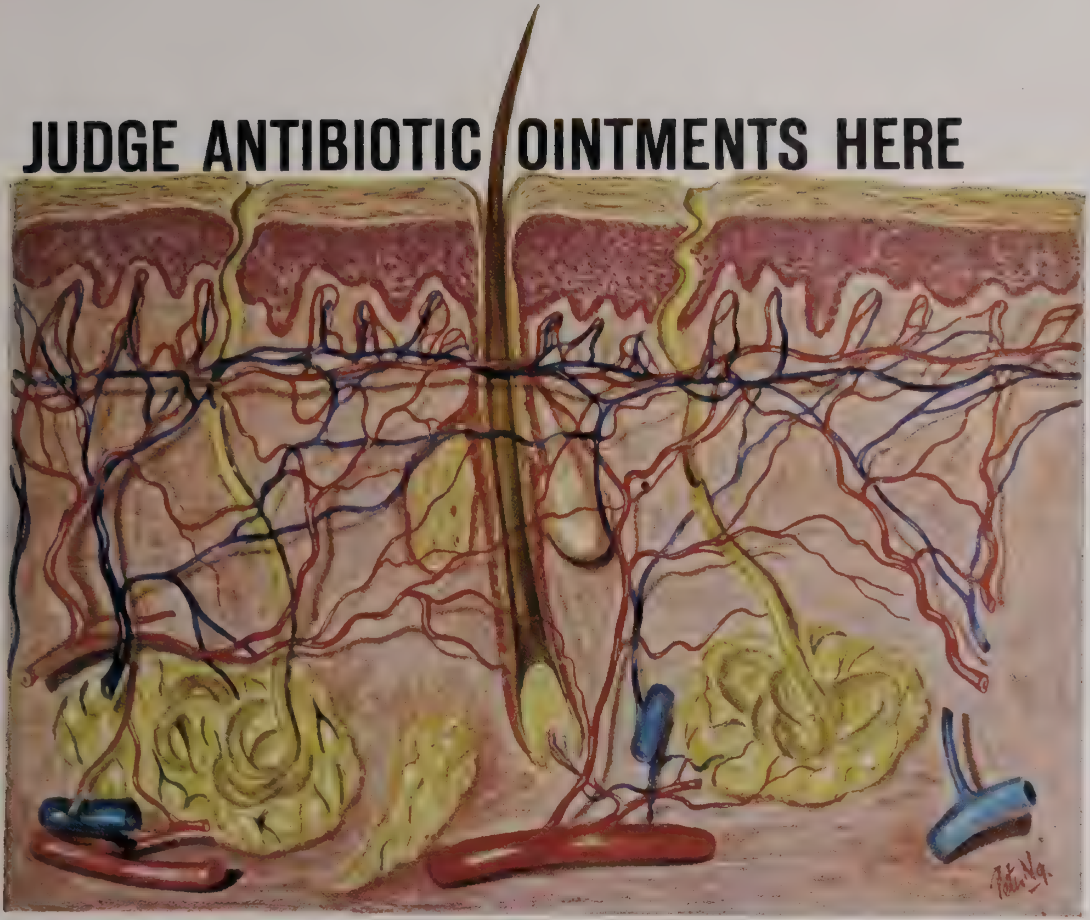
*Chief of Urology, Veterans Administration Hospital.

Reference

1. Abrams, H. L.: Radiology 82:217, 1964.

JUDGE ANTIBIOTIC OINTMENTS HERE



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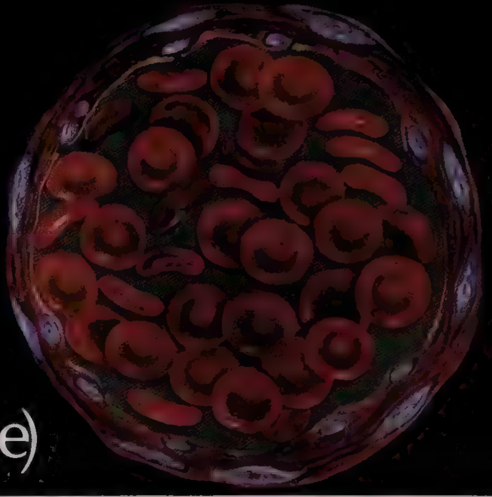

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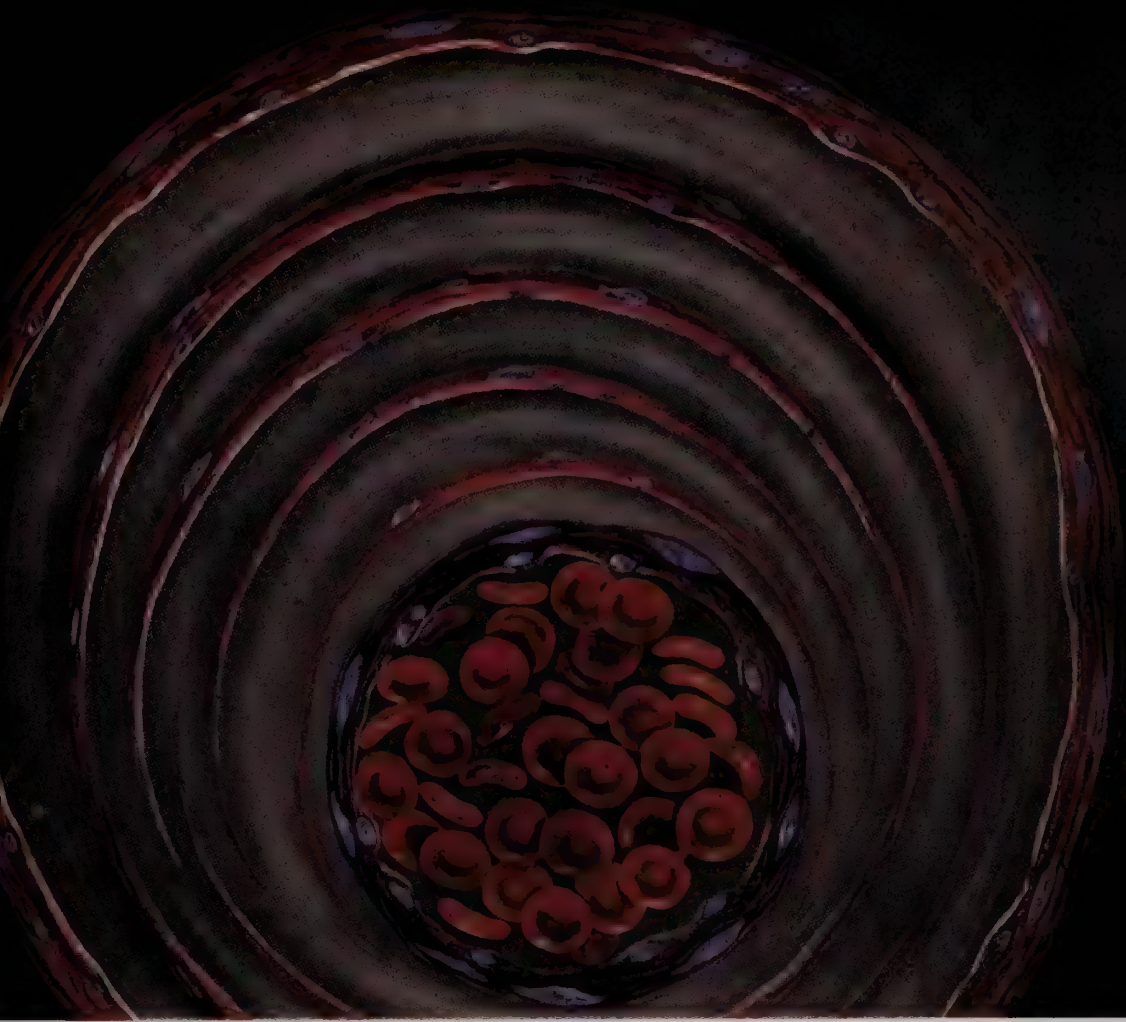

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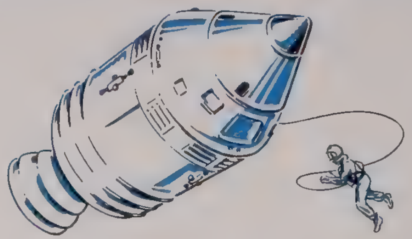

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Fracture Conference

Problems in Initial Treatment of Multiple Fractures*

Dr. Clarence R. Petrie:

After an automobile accident involving four teen-agers, all four were admitted simultaneously. We will present two of these cases because they represented challenging problems in the initial treatment planning for multiple fractures.

Case 1

The first case is that of a 17-year-old boy who was in the rear seat of a car that struck a bridge at an alleged speed of 90 miles per hour. During impact, he was ejected from the seat. In the emergency room, it was obvious that he had bilateral closed fractures of both femurs and an open fracture of the right ulna. Roentgenograms showed a comminuted midshaft fracture of the left femur with large butterfly fragments (Figure 1 left) and a severely comminuted midshaft fracture of the right femur with numerous splinter fragments (Figure 1 right). He also had a Monteggia type fracture of the right forearm (Figure 2), with the

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*Fracture Conference held April 15, 1968.

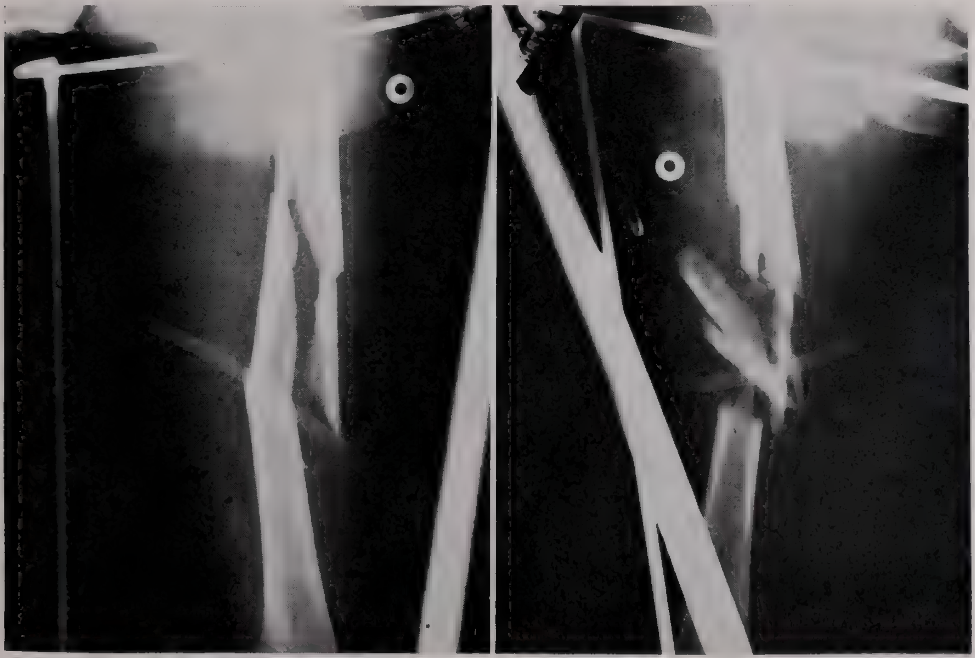

Fig. 1—(Case 1). Roentgenograms of femurs made in emergency room.

neck of the radius fractured rather than dislocated. A jagged laceration was present over the ulnar fracture site and extended up to the olecranon. In the femoral fractures, the soft tissue nerves and vessels were found to be intact.

The patient was in overt shock. With resuscitation well established, using blood and Ringer's lactate solution, he was taken to the operating room where, under general anesthesia, Steinmann pins were inserted into both tibial tubercles and traction was applied. The forearm wound was thoroughly cleansed and widely debrided, and the radius was examined. The annular ligament was found to be intact; therefore the head of the radius was left in situ. Internal fixation of the ulna was achieved by the insertion of a Rush intramedullary nail, which facilitated the reduction of the radial fracture as well. The arm was put in a Robert Jones dressing and the patient was taken to his room and placed in bilateral leg traction.

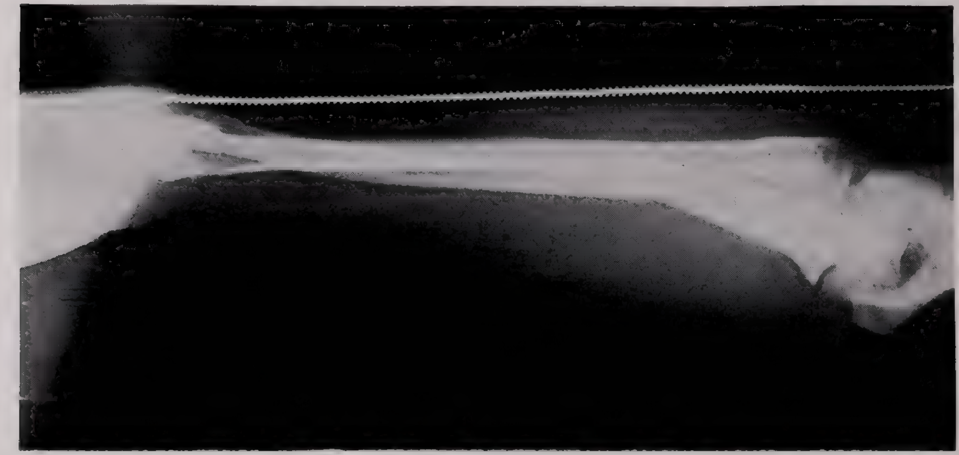

Fig. 2—(Case 1). Right forearm on admission.

Dr. Harry F. Jones:

The wound of the ulnar fracture was excised, debrided, and cleansed of all debris. Obviously dead material was removed, and then we proceeded to fix the fracture (Figure 3). The skin was packed open on the wound over the ulna. Now may I have some comments from the staff on these fractures of both femurs and the forearm. Dr. Coventry?

Dr. Mark B. Coventry:

When there are fractures of an upper and a lower extremity you really have more to worry about, because we hope eventually to have the patient ambulatory, and we would like to have a limb that can manipulate crutches. I think you have done the right thing in taking care of the forearm definitively and putting the femurs in traction with the patient in bed, perhaps starting him on anticoagulants, to wait it out in traction.

Dr. Jones:

It was my thought at the time that, if this had been a closed fracture, with everything else being equal, I would not have opened it. But, in a fracture like this in a boy of this age, one would probably have to open it sooner or later. I would have left it for two days or until things stabilized. When we saw him, he had lost a considerable amount of blood; but, once we got him resuscitated, we proceeded with the surgery.

Dr. Paul R. Lipscomb:

Dr. DePoali, who is visiting with us and has just finished two years in the

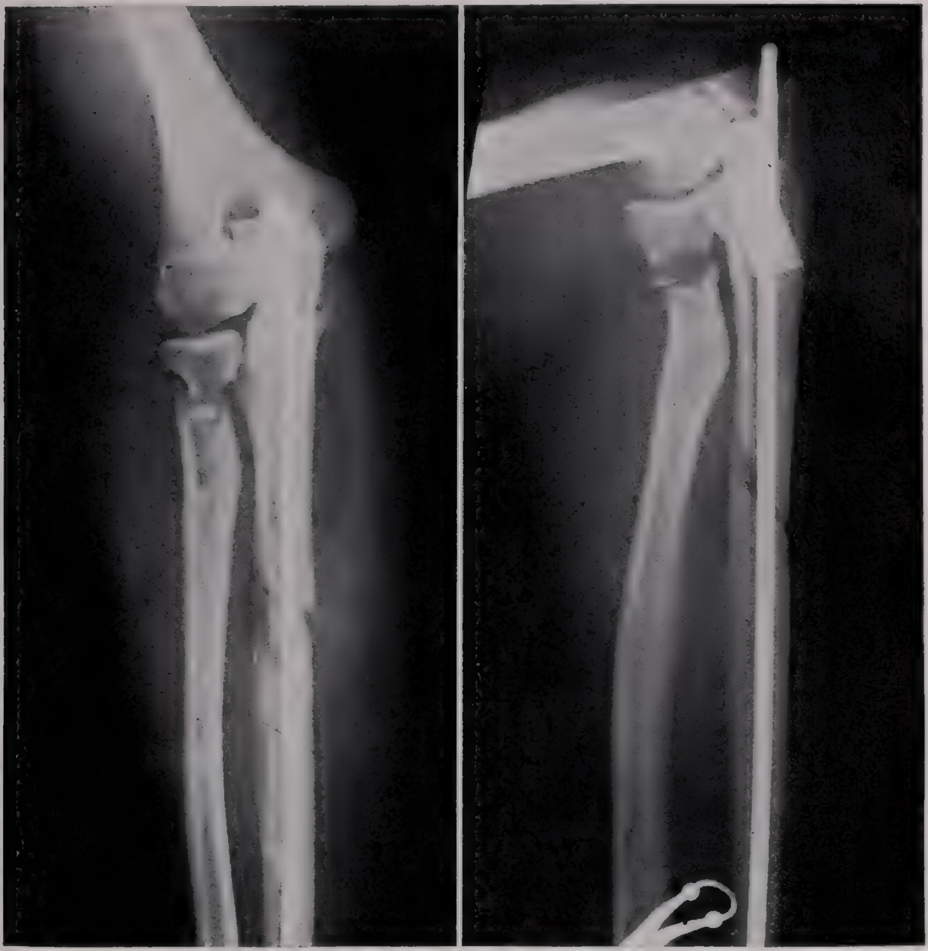

Fig. 3—(Case 1). Forearm after fixation of fracture.

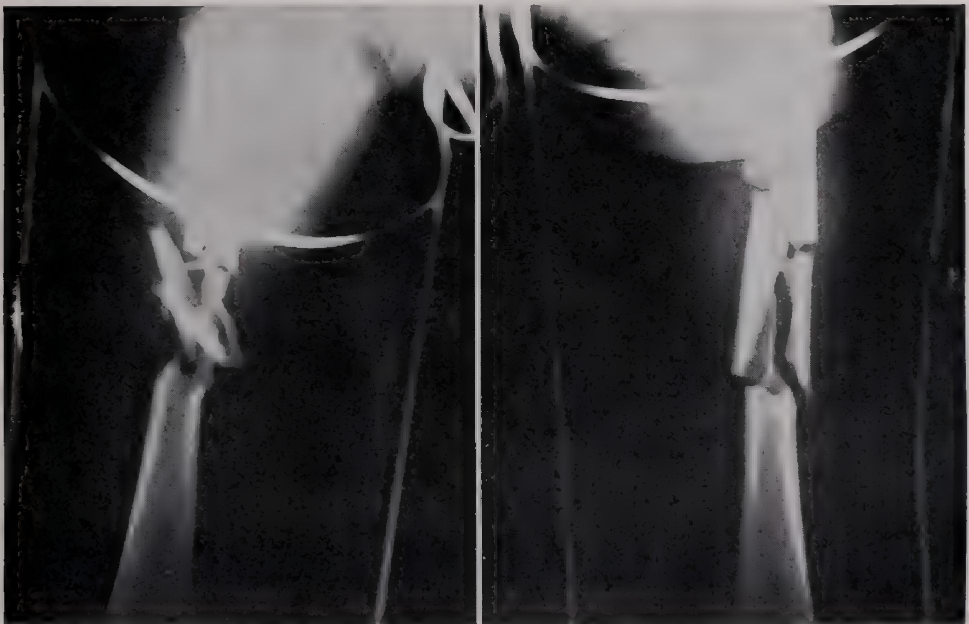

Fig. 4—(Case 1). Femurs after about three weeks in traction.

Army, made the point that if, in a case of fractures or multiple injuries like this, you can keep from giving a general anesthetic the situation remains clearer. For example, such things as a ruptured spleen may be hidden by a general anesthetic. It may have been safer to do this under axillary block and insert the pins under local anesthesia, even if it would have taken time.

Dr. Jones:

I would agree with this; but at that time it was 2:00 or 3:00 a.m. and the anesthesiologist thought it better to have the patient asleep than to do this under a block. I would personally agree entirely with you. I wonder if I could get some views on whether or not we should have excised the head of the radius.

Dr. Ronald L. Linscheid:

I would not particularly want to excise the radial head. I have treated some injuries like this in which, even if you do have a stable ulna, you get some angulation at the fracture site in the radial head. Because this has happened to me, I would probably transfix that radial head with a Kirschner wire through the distal humerus.

Dr. Jones:

I felt this radial head with my hand. The annular ligament was entirely

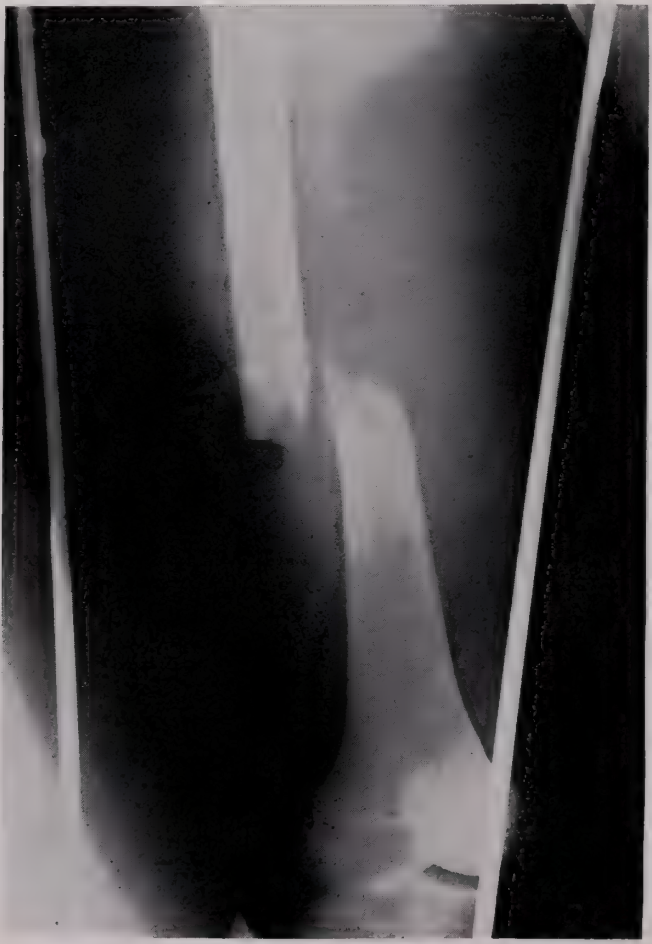

Fig. 5—(Case 2). Right femur on admission.

intact—it had not been injured at all—and at the time the situation seemed to be safe from late dislocation.

Dr. Einer W. Johnson, Jr.:

We have mentioned this before and I think it should be mentioned again that the thorough debridement of the compounding wound is essential. If this fracture had become infected, you would have had serious trouble. I personally think that it is correct to pack the wound open, as you have done, and proceed with delayed primary closure or secondary closure at some future date when you know you have good control of whatever bacteria may be there. It seems to me you have lost nothing by doing it this way as compared to closing the wound primarily, even though antibiotics are available to help you. Primary closure is recommended by some. I think it is far better to pack it open and close it at another time.

Dr. Jones:

I do not think anyone would close a very dirty wound in a case like this. This boy was thrown down an embankment into the mud and dirt, and the wound was quite a mess when he arrived. These roentgenograms of the femurs in traction were made about three weeks postoperatively (Figure 4).

Dr. Coventry:

I would like to comment on what Dr. Lipscomb said about initial shock. To make it a little more complete, do not forget the fat embolism problem which is always a potent one in multiple injuries 24 or 48 hours, and even three or four days later. The initial anesthesia can mask or even aggravate that embolism. So it is not only shock but also fat embolism you have to contend with.

Dr. Petrie:

Case 2

A 17-year-old boy was the driver of this automobile when it struck the bridge. He was not thrown out of the car but was pinned and had to be removed forcibly. On examination in the emergency room, he was in shock; he had an open fracture of the midshaft of the right femur with loss of overlying tissue, and the proximal fragment protruded from the wound. This can actually be seen on the roentgenogram (Figure 5). He also had a closed fracture of the left forearm involving the distal third of the ulna and the middle third of the radius (Figure 6).

The patient was resuscitated and, when hemodynamic stability was attained, was taken to the operating room for wide debridement of the thigh wound and internal fixation by the use of a Mueller compression plate (Figure 7 left and center). The wound was packed wide open

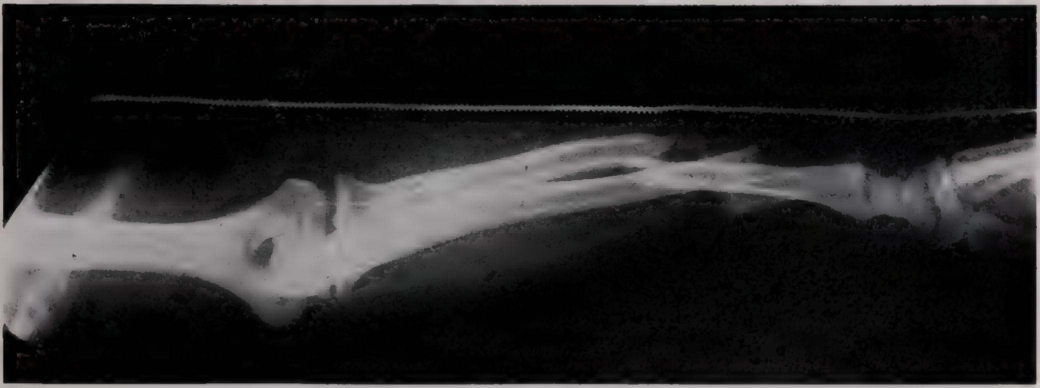

Fig. 6—(Case 2). Left forearm on admission.

and dressings were applied. We then proceeded to do open reduction and internal fixation of the left forearm. Mueller compression plates were applied to both ulna and radius (Figure 7 right). The left forearm was severely swollen and was placed in a Robert Jones dressing with a Bunnell dressing on the hand.

Two days postoperatively the patient was returned to the operating room and the thigh wound was inspected and found to be clean and noninfected. It was repacked. Five days postoperatively the thigh wound was once again inspected. In the interim there had been no evidence of infection and the wound was found to be clean. Due to soft tissue loss at this site, local skin flaps had to be mobilized to close the soft tissue defect (Figure 8). Fifteen days postoperatively the wound was again inspected and once again there was no evidence of infection. A hip spica was applied and the patient was dismissed, to return in six weeks for reassessment.

Dr. Jones:

In my opinion the wounds were well healed. I wonder if Dr. Coventry would like to comment on this case?

Dr. Coventry:

I think you have done what I would do. You have a wound that was compounded. This alters your plan of treatment. You have to get at the wound, and while you are in there, I have always found that there is no added risk, and it certainly is a tremendous boon to the patient, if you can secure the fracture at the same time. Providing everything else is equal, putting a plate and

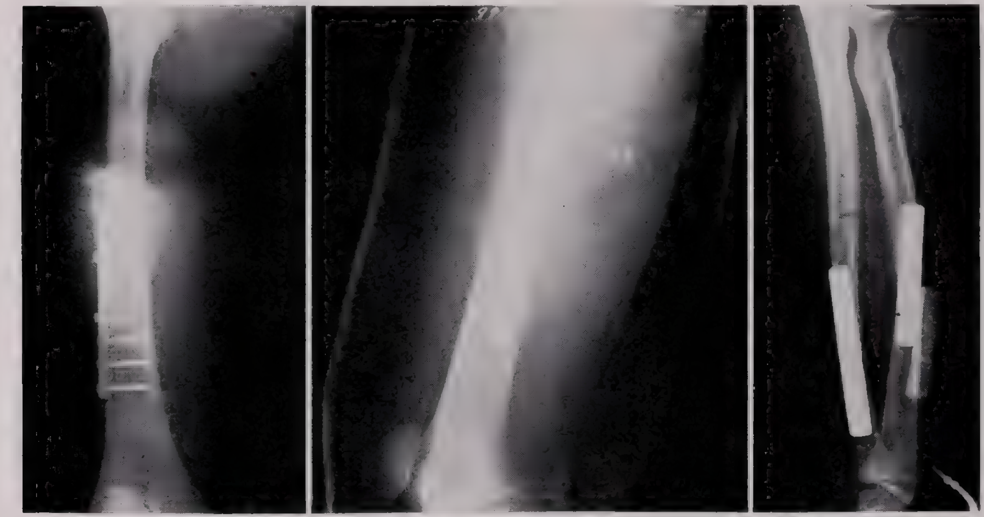

Fig. 7—(Case 2). After application of Mueller compression plates. Left and Center, Femur. Right, Forearm.

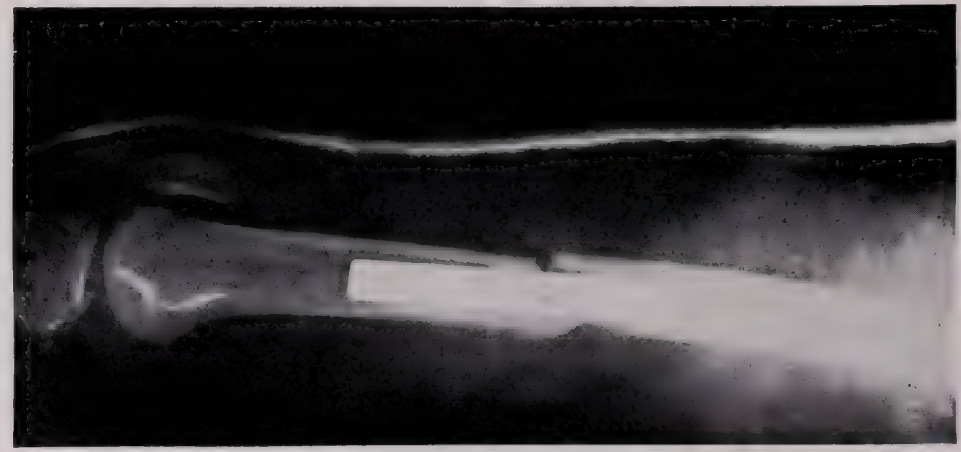

Fig. 8—(Case 2). Femur five days postoperatively, at time of wound closure.

screws into an acute fracture is no offense and is a very good way to avoid a bad situation for the patient.

Dr. Jones:

I spent two and a half hours debriding the patient's wound and 15 minutes applying this plate. I think it would be wrong if it were the reverse. This wound was either going to become infected or it was not going to become infected. The addition of a plate, as far as I was concerned, did not endanger the situation. I think the thoroughness of the debridement was the important thing.

Dr. Richard S. Bryan:

As a point of criticism on the technique of insertion of the Mueller compression plate I should like to state that the distal compression screws should not go through both cortices. You run a risk of fracture at that point, which should be avoided. You need only one cortex for application of the compression apparatus.

Dr. Jones:

I am aware of this.

Dr. Bryan:

Second, with reference to the plating of forearm bones, there are a number of articles in the English literature which criticize the use of these four-hole plates. I tend to use them, but I think the opponents make their point. Use of three screws on each side gives a lot more fixation than two, and your fulcrum screw on the radial fracture appears to be almost in the fracture itself.

Dr. Jones:

Even though this fracture is pretty far distal on the shaft, we had a problem attaching even this size of plate.

Dr. Bryan:

You could have gotten three screws on that one going down the radial shaft. It could be a little difficult, but it would be possible. The English are critical of using less than six screws. This is the third point: they may be right and they may be wrong, but it is a point to consider. It appears that there is not much compression on the radius.

Dr. Jones:

There is no compression on that at all. I ran into a situation in this fracture which never happened to me before, but I put the Rush pin down the ulna and the compression plate on the radius. However, for some reason or other, we got off track and the Rush nail penetrated the ulnar cortex. Try as I might, I could not get the nail to return in the right direction. It was then that we decided to plate this bone also.

Dr. William H. Bickel:

Another point Dr. Mueller makes is that the end screws in the plate—this would have to be in a six-hole plate—should not go through both cortices because some pathologic fractures occur when the screws are put through both cortices. It is all right to put a longer flare on the end of the plate or to put a screw through one cortex.

Dr. Bryan:

One last point, so that somebody can come back and step on me: Why did you not put two plates on the femur?

Dr. Jones:

I really did not think that I needed to. It was stable as a rock the way it was. I thought that if it did get infected I would have to remove the plate. I did not put this boy in a spica cast or anything; I put him in a Robert Jones dressing, in which he remained for approximately 15 days while we were observing his wounds. There was no problem whatsoever with instability. He was moved from a cart to the bed and was frequently on a bedpan. All I can say is that at operation I thought this fracture was compressed sufficiently.

Dr. Bryan:

From looking at the roentgenograms, you are not sure how far the screws go through, or of the even seating of the screw heads. This I have found myself: I measure them, I put them in, and I think I have beautiful fixation; then I look at the postoperative roentgenograms and wonder why I did not make that a quarter, or at least an eighth, of an inch longer. I am sure that I measured it as carefully as I could and got as excellent fixation as possible. Once in a while the fixation will fail; then we regret it about six to eight weeks later.

Dr. Johnson:

These last two cases represent a problem in the initial treatment in the trauma of these two boys. They were both in a serious automobile accident. The point I would like to make is that I think you glossed over the principal problem: the prevention of infection. Had either of these wounds become infected, you would have been in deep trouble. You stated briefly that you spent two and a half hours debriding the wound and 15 minutes applying the plate. It should be reiterated that you did a thorough wound toilet, which is to be expected, but we must emphasize that point. We have often seen wounds treated elsewhere that are not well debrided and come to us dirty. The thing to be striven for in these cases is wound toilet, excellent debridement, and healing without infection.

Dr. Jones:

One other point I should have brought out more clearly is that I consider this a staged debridement. You debride it initially and then again at two days, at four days, and, if necessary, at six days. You have to evaluate such a wound every other day, or every day, depending on how you do it. I do not think anyone can look at a wound and say, "Now I have thoroughly debrided that," or "There is no more devitalized muscle, skin, or bone, or some such thing." We returned this boy to the operating room, did a full preparation and scrub, and thoroughly examined this wound inside and out rather than just glancing at it on the ward and saying it looked clean.

Dr. Johnson:

This is the point that I consider interesting.

Dr. Jones:

Our time is up. These cases illustrate the problems in initial care of the multiply-injured patient—attention to proper resuscitation and control of shock, definitive care only when the patient is hemodynamically stable, and, probably most important of all, thorough debridement and cleansing of compound wounds.

Harry F. Jones, M.D.*
Clarence R. Petrie, M.D.*
Einer W. Johnson, Jr., M.D.*
Rochester, Minnesota

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*From the Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

Memory Aid

"Doctor," she says, "I have written a list
Of my symptoms, for fear I'd forget them.
They're here in my bag, if I only can find
The paper on which I have set them.

"Yes, here they are, doctor; I have here the list
Of the things that I've carefully noted:
A pain that begins in the small of my back
And my being so terribly bloated,

"And a dozen loin chops and it hurts me to breathe
And a couple of pounds of tomatoes
And a rash on my chest and a small piece of cheese
And chills and a sack of potatoes."

Richard Armour: The Medical Muse, 1963.

Objective vs Subjective

If the sense of sight is more objective, the sense of hearing is more subjective, and it is through this latter sense, by means of dialogue, that the physician's "I" merges with the patient's "you," as von Weizsacker pointed out. This is why the clinical case history achieved in such a manner has the same value that experimental observations have in the natural sciences. Every disease is eminently biographical, even infections and degenerative organic affections, and its configuration, or Gestalt, depends not only on the biological dimension of the individual biography, but on the totality of the biography, on the personal dimension of human existence.*

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*The Patient's Progress, Edited by Felix Marti-Ibanez, M.D., 1962.

Worry

Now psychologists think they have found what professional people worry about. At the age of 26, they say, the principal worry is about making a good impression on people, at 30 about job security and economic problems, at 38 about health and at 41 about politics. At 42 marital problems are in the fore, and by 45 professional men and women concentrate on worrying about giving up lifelong ambitions. After that, health again becomes the chief preoccupation.

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CONTRAINDICATIONS: Central nervous system depression from drugs (barbiturates, alcohol, narcotics, analgesics, antihistamines); bone marrow depression; urinary retention; pregnancy; glaucoma. Do not give in combination with MAOI drugs because of possible potentiation that may even cause death. Allow at least 2 weeks between therapies. In such patients therapy with TRIAVIL should be initiated cautiously, with gradual increase in the dosage required to obtain a satisfactory response.

WARNINGS: Patients should be warned against driving a car or operating machinery or apparatus requiring alert attention, and that response to alcohol may be potentiated.

PRECAUTIONS: Suicide is always a possibility in mental depression and may remain until significant remission occurs. Supervise patients closely in case they may require hospitalization or concomitant electroshock therapy. Untoward reactions have been reported after the combined use of antidepressant agents having various modes of activity. Accordingly, consider possibility of potentiation in combined use of antidepressants. Not recommended for use in children. Mania or hypomania may be precipitated in manic-depressives (perphenazine in TRIAVIL seems to reduce likelihood of this effect). If hypotension develops, epinephrine should not be employed,as its action is blocked and partially reversed by perphenazine. Caution patients about errors of judgment due to change in mood.

SIDE EFFECTS: Similar to those reported with either constituent alone.

Perphenazine: Should not be used indiscriminately. Use caution in patients with history of convulsive disorders or severe reactions to other phenothiazines. Likelihood of untoward actions greater with high doses. Closely supervise with any dosage. Side effects may be any of those reported with phenothiazine drugs: blood dyscrasias (pancytopenia, thrombocytopenic purpura, leukopenia, agranulocytosis, eosinophilia); liver damage (jaundice, biliary stasis); extrapyramidal symptoms (opisthotonos, oculogyric crisis, hyperreflexia, dystonia, akathisia, dyskinesia, parkinsonism) usually controlled by the concomitant use of effective antiparkinsonian drugs and/or by reduction in dosage, but sometimes persist after discontinuation of the phenothiazine; severe acute hypotension (of particular concern in patients with mitral insufficiency or pheochromocytoma); skin disorders (photosensitivity, itching, erythema, urticaria, eczema, up to exfoliative dermatitis); other allergic reactions (asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions); peripheral edema; reversed epinephrine effect; endocrine disturbances (lactation, galactorrhea, disturbances of menstrual cycle); grand mal convulsions; cerebral edema; altered cerebrospinal fluid proteins; polyphagia; paradoxical excitement; photophobia; skin pigmentation; failure of ejaculation; EKG abnormalities (quinidine-like effect); reactivation of psychotic processes; catatonic-like states; autonomic reactions such as dryness of the mouth, headache, nausea, vomiting, constipation, obstipation, urinary frequency, blurred vision, nasal congestion, and a change in the pulse rate; hypnotic effects; pigmentary retinopathy; corneal and lenticular pigmentation; occasional lassitude; muscle weakness; mild insomnia; significant unexplained rise in body temperature may suggest intolerance to perphenazine, in which case discontinue. Antiemetic effect may obscure signs of toxicity due to overdosage of other drugs or make diagnosis of other disorders such as brain tumors or intestinal obstruction difficult. May potentiate central nervous system depressants (opiates, analgesics, antihistamines, barbiturates, alcohol), atropine, heat, and phosphorous insecticides.

Amitriptyline: Careful observation of all patients recommended. Side effects include drowsiness (may occur within the first few days of therapy); dizziness; nausea; excitement; hypotension; fainting; fine tremor; jitteriness; weakness; headache; heartburn; anorexia; increased perspiration; incoordination; allergic-type reactions manifested by skin rash, swelling of face and tongue, itching; numbness and tingling of limbs, including peripheral neuropathy; activation of latent schizophrenia (however, the perphenazine content may prevent this reaction in some cases); epileptiform seizures in chronic schizophrenics; temporary confusion, disturbed concentration, or transient visual hallucinations on high doses; evidence of anticholinergic activity, such as tachycardia, dryness of mouth, blurring of vision, urinary retention, constipation, paralytic ileus; agranulocytosis; jaundice. The antidepressant activity may be evident within 3 or 4 days or may take as long as 30 days to develop adequately, and lack of response sometimes occurs. Response to medication will vary according to severity as well as type of depression present. Elderly patients and adolescents can often be managed on lower dosage levels.

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Case Reports

Corrosive Esophagitis

Acute Management with a Case Report of Early Surgical Intervention

Case Report

A 41-YEAR-OLD paranoid schizophrenic patient was transferred to Minneapolis Veterans Administration Hospital for management of an acute corrosive esophagitis following an attempted suicide by lye ingestion the evening prior to his transfer. On admission he was found to have a severe burn of both the anterior and posterior oral cavity. Treatment was initiated with antibiotics and steroids; a small feeding tube was passed and a tracheostomy was performed. Within 24 hours of admission, substernal pain and a chest x-ray led to the diagnosis of esophageal perforation with mediastinitis and empyema. Approximately 60 hours following the lye ingestion, surgical exploration revealed his esophagus to be necrotic from the level of the second tracheal cartilage to the gastroesophageal junction and his stomach necrotic over the proximal 80%, with several areas of necrosis. An area of perforation of the esophagus into the right pleural cavity was found, and 2.5 liters of fluid were drained from the right pleural and peritoneal cavities. A subtotal gastrectomy, a total esophagectomy, with cervical esophagostomy, and a gastrostomy were performed. The patient tolerated the procedure well. He continued to have a low-grade fever but showed overall improvement until the sixth post-operative day when he suffered a massive hemorrhage and expired. Post-mortem examination showed a suppurative mediastinitis with massive great vessel hemorrhage as the cause of his demise.

Etiology

Corrosive esophagitis appears as the result of the ingestion of some irritating acid or alkali with a frequency[31] of 8.9/100,000 general hospital admissions. It has a higher incidence[14,31] among the lower income groups, the southern states and the negro population. It is seen more frequently below the age of 15, with a greater proportion of males than females; but within the adult population there is an equal distribution between the sexes, the female suicides matched by the male "alcoholic accidents." The agents commonly involved include[33]: NaOH, KOH, phenol, ammonia, formaldehyde, lysol, sulfuric acid, nitric acid, lactic acid, potassium, permanganate, iodine and bichloride of mercury. Lye (NaOH) is[23] the most frequent offender and the most serious, for while acid will produce a coagulative necrosis leading to early eschar formation, alkali, due[31] to its hydroscopic, saponifying, and protein solvent properties, will produce a liquefying necrosis enabling penetration to deeper layers.

Pathology

The severity of the lesion produced depends[10,34] directly upon the corrosive agent swallowed: its nature, concentration, quantity and the duration of its contact with the tissues. A 3.8%[9] (1 N) solution of NaOH applied for 10 seconds to the esophagus will necrose the mucosa, the submucosa, and some of the inner longitudinal muscle fibers, while a 22.5% (7 N) solution in the same time will extend necrosis through the whole esophageal wall and affect the periesophageal tissues. The significance of these values is obvious when it is realized that household cleaning and washing powders typically have from 8 to 50% NaOH as their chief ingredient.

The usual[34] areas of esophageal involvement are the cricopharyngeus, the crossing of the left main bronchus and the cardia. The upper esophagus is the most frequently involved, while the lower esophagus is usually the most seriously involved, presumably due to reflex spasm at the cardia. The lesion develops in a characteristic sequence[3,5,14]: within the first 24 hours there develops epithelial destruction, edema and congestion of the entire wall. Within 48 hours this inflammatory infiltrate leads to thrombosis of submucosal, vessels, giving rise to local areas of gangrene with sloughing of the surface layers. Bacterial invasion follows, leading to intramural abscess formation and final chronic inflammatory change. Re-epithelialization is often incomplete at six weeks, while stricture formation is discernible after the second week.

TABLE

Complications of the Injury

Acute Phase:[30]		Late Phase:[6]
Mediastinitis	20%	Stricture
Ulceration into aorta or trachea	20%	Perforation of the esophagus (secondary to esophagoscopy or dilatation)
Perforation of the esophagus	15%	Aspiration pneumonia
Peritonitis	15%	Operative risk from reconstructive surgery
Bronchopneumonia	14%	Carcinoma from the old stricture line[33,6,7]
Perforation of the stomach	10%	
Edema of the larynx	6%	
Acute Mortality is Variously Reported:		
Holinger and Johnston[15]	3.1%	
Stumboff[30]	27.0%	
Hung et al.[17]	36.6%	

Treatment

The management of corrosive esophagitis remains controversial. Treatment generally depends[9] upon the severity of the burn, the systemic reaction to the injury and the complications that develop. Proper therapy[9] includes an initial control of shock, restoration of electrolyte balance, maintenance of nutrition, antibacterial therapy, and ultimately, a repair of the esophageal lesion itself.

Acute Phase

Attempt Neutralization

(1) Alkali by 2% acetic acid, vinegar or citrus juices. (2) Acid by olive oil, milk, magnesium oxide or egg white (not $NaHCO_3$, because the gas formed will stimulate distention and vomiting). (3) Gastric lavage in acid ingestion (contraindicated in alkali ingestion). However, it has been shown[10] that attempts to neutralize later than one minute after ingestion of the offending agent had no effect on the clinical course of the patient, and even within one minute, it did not prevent injury to the tissues.

Treat Tracheostomy

Indicated to maintain ventilation in increasing laryngeal edema.

Put Esophagus at Rest

(1) Discontinue all oral feedings. (2) A small feeding tube may be introduced[13,29] to maintain a patent lumen and provide a route for nourishment, but some[10] feel the increased trauma of the tube and its stimulus to nausea and vomiting contraindicate its use.[10,33,34] (3) A gastrostomy may be created to provide nourishment.

Antibiotics

To control secondary infections and reduce scarring one million units of penicillin and one gram streptomycin per day have been used.[9] However, reports[19] indicate the antibiotics promote early granulation tissue and hasten its maturation, resulting in earlier stricture formation.

Steroids

To reduce inflammation and subsequent scarring, use of cortisone equivalent to 420-560 mg/day for a 70-kilo human has been shown[27] to reduce scarring, and prednisone at 4 mg/kilo in divided doses has been successfully used clinically.[19,9] However, these steroids must be used less than 48 hours after the insult and preferably less than 24 hours to prevent scarring.[27,34] The steroids in decreasing inflammation tend to increase the incidence of suppurative infections and must always be used in conjunction with antibiotics.[26,27,28] Steroids further (even with antibiotics) tend to increase the incidence of perforation and hence are contraindicated in very severe burns and in gastric ulcerations.[28]

Anticholinergic agents and antacids are recommended in steroid therapy.[28]

Daily x-rays of the mediastinum (for the first two weeks) for early detection of perforation are recommended in steroid therapy.[28]

Patent Lumen

A string can be swallowed to maintain a patent lumen and to act as a guide for examinations or dilatations.[33]

Symptomatic Relief

H_2O_2 oral care; medications for relief of pain; olive oil and other soothing agents may be sipped cautiously.

Intermediate Phase

In the intermediate phase, therapy is directed to the prevention of contracture. There generally are three approaches to the problem.[33] 1) Early dilation to prevent collagen fiber contracture: (Salzer, Bokay, Martin and Arena, Gellis and Holt, Crowe, Kernodle, and Holinger). 2) Dilation after contracture has started to form: (Stumboff, Vinson). 3) No dilations in the belief that all established strictures of the esophagus are surgical problems: (Burford).

Late Phase

Treatment in the late phase involves the restoration of esophageal function by the relief of strictures that have developed. There are several techniques available: Blind bouginage, direct bouginage (using Jackson dilators) through an esophagoscope, bouginage over a string guide, retrograde bouginage utilizing a gastrostomy and "endless string," pneumatic bougies placed under fluoroscopic control, and surgical restoration of the damaged tract.

Comment

This case in unusual in that it represents an attempt at early, radical, surgical treatment for corrosive esophagitis. In retrospect it is apparent the esophagus was non-viable and the only possible treatment was the removal of the necrotic tissue; it is unfortunate this was not realized earlier. Contamination of the mediastinum (perforative[4,11,14,20] or otherwise[18]) with subsequent suppuration has an untreated mortality[11] of 84% that can be reduced by surgical intervention to 15 to 30%. Such values demonstrate the place for early consideration of such surgery in those patients whose injury is so severe as to preclude a more conservative therapeutic regime. In these select cases, this early radical surgery may be life preserving and should consequently be given careful consideration.

Michael Hennessy*
Minneapolis, Minnesota

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*University of Minnesota Medical School, Third Year (Now in his fourth year).
References may be secured from the author.

The only way to entertain some folks is to listen to them.—Frank McKinney Hubbard

Abstracts

NONINSTRUMENTAL PERFORATIONS OF THE ESOPHAGUS

Perforations of the esophagus often lead to a high morbidity and mortality, particularly when recognized late. A 30% mortality is reported among the series of 22 patients with noninstrumental perforation of the esophagus. Perforations due to injection of a sharp foreign body responded well to treatment, whereas spontaneous postemetic perforation and rupture of the esophagus carry an extremely grave prognosis, with six to eight patients succumbing to this disease. Treatment of the foreign body perforations of the cervical esophagus consisted of removal of the offending foreign body and occasionally cervical drainage. Treatment of the postemetic thoracic esophageal perforation included surgical drainage and attempts at closure of the esophageal perforation.

Theodore A. Peterson, M.D.
Minneapolis, Minnesota

Adam R. Wychulis, M.D., et al.: Noninstrumental Perforations of the Esophagus. Dis Chest 55:3:190, 1969.

THERMOGRAPHY IN BREAST CARCINOMA

Isard et al. have studied a large series of women constituting approximately 2700 patients in whom thermograms were carried out. The tests were negative in 69 percent and positive in the rest.

The significant finding seems to be that in the proven malignant lesions thermograms were positive in 72 percent, whereas in the benign group they were positive (incorrectly diagnostic) in 61 percent.

From this the authors justifiably concluded that they were "unable to differentiate the benign from the malignant pattern by this technique."

In using the thermogram technique, however, it might be favorably said that "any departure from the baseline pattern of an individual should serve as a warning for some disease process."

Only for an institution or an individual who is carrying out a large series of breast examinations serially would it seem economically and scientifically feasible to institute this type of laboratory evaluation.

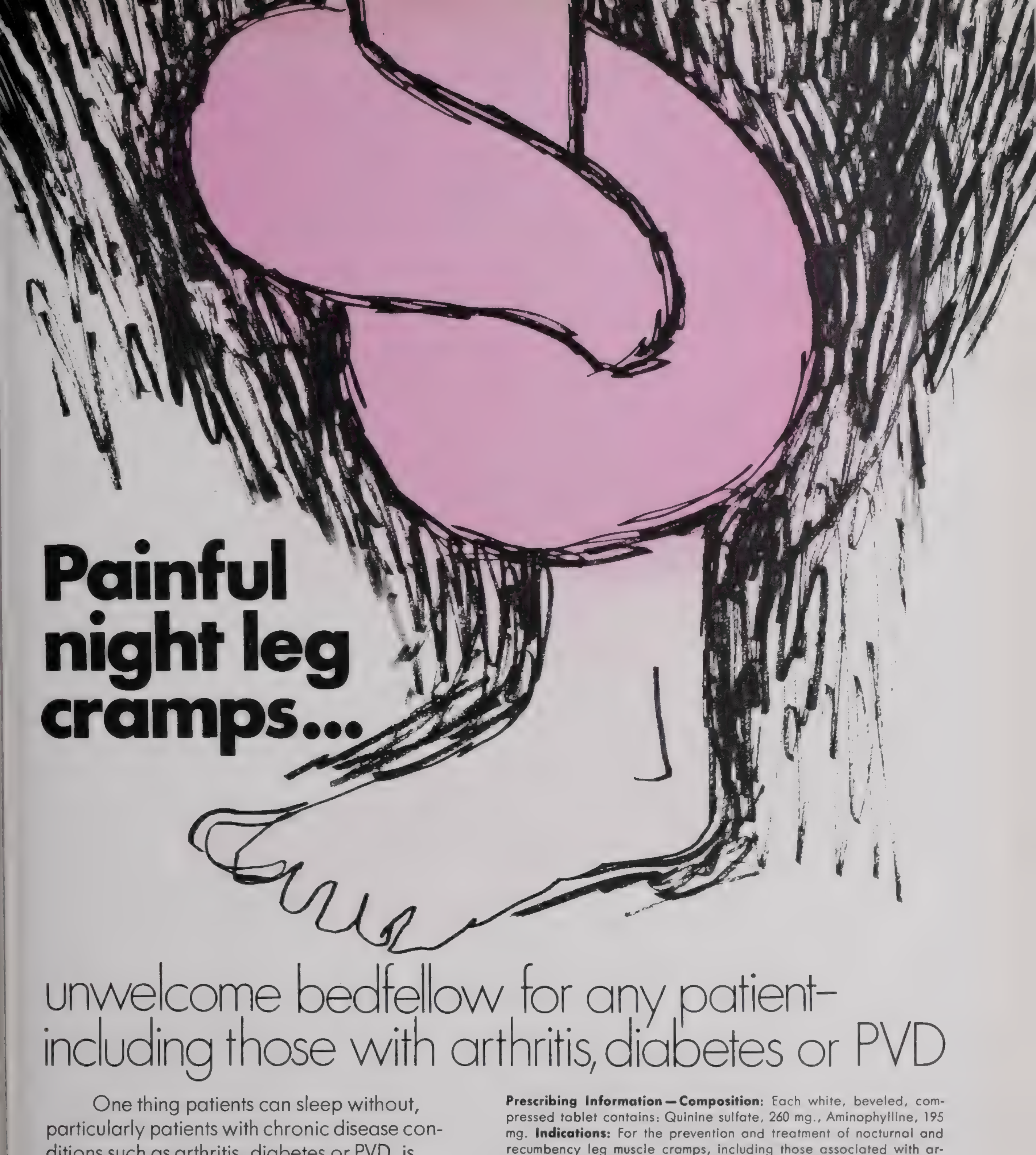
Carl O. Rice, M.D.

INSTRUMENTAL PERFORATION OF ESOPHAGUS

Esophageal perforation occurred in 33 of 8,038 patients who underwent gastrointestinal endoscopic procedures at Mayo Clinic (0.4%). The percentage for patients undergoing the esophagoscopy was 0.8%. Perforations of the cervical portion of the esophagus were more common but less serious than those of the thoraco-abdominal esophagus. Perforations occurred most commonly at the site of either benign or malignant esophageal strictures and were most frequently caused by excessive dilatation without satisfactory guide, bougienage or biopsy, but beyond visual range. The most helpful diagnostic tests were x-rays of the neck or thorax. Results were best when treatment was initiated promptly and pursued aggressively with use of antibiotics, surgical drainage and elimination of esophageal obstruction.

Theodore A. Peterson, M.D.
Minneapolis, Minnesota

Adam R. Wychulis, M.D., et al.: Instrumental Perforation of Esophagus. Dis Chest 55:3:184, 1969.

**Painful night leg cramps...**

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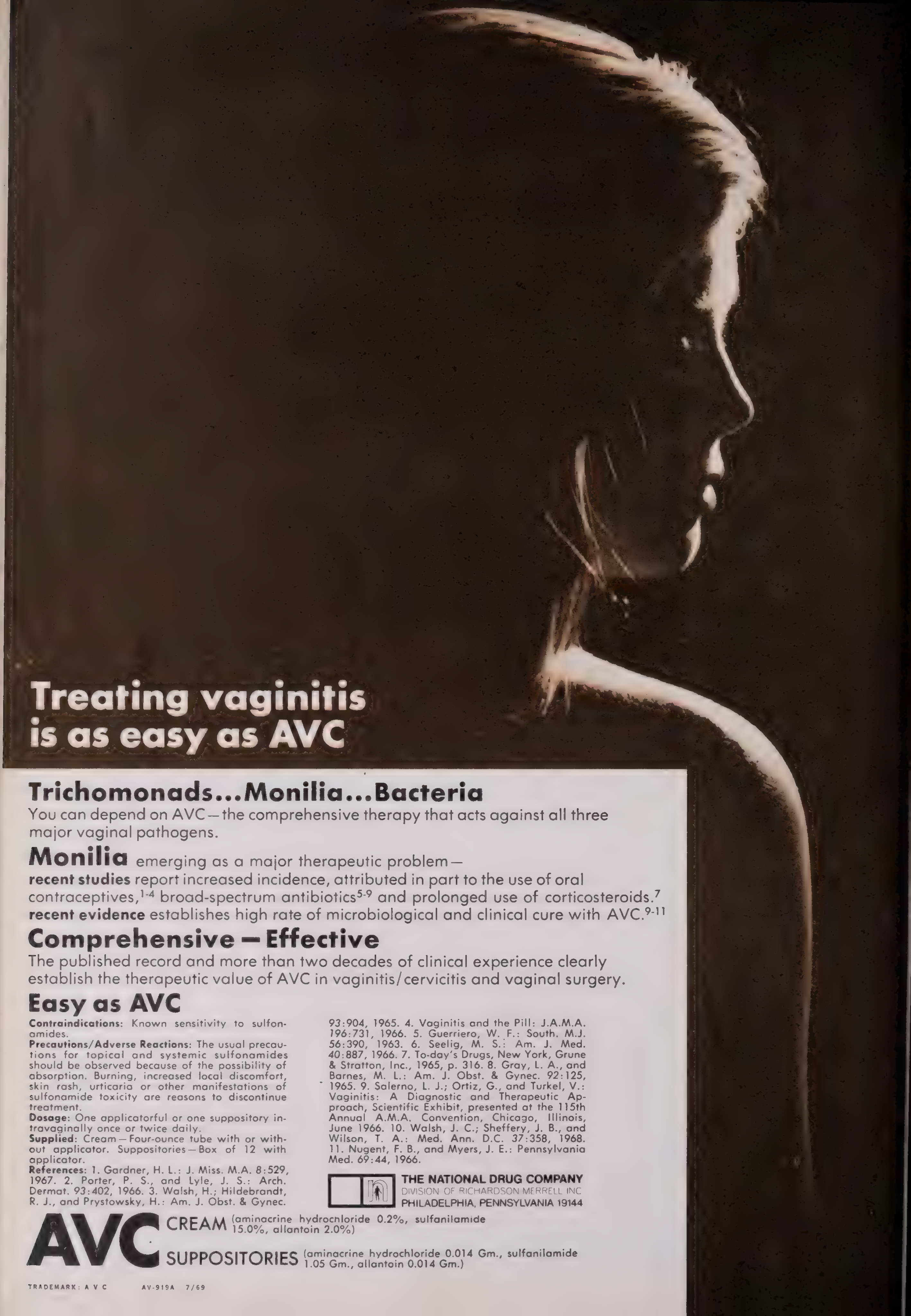

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recent studies report increased incidence, attributed in part to the use of oral contraceptives,[1-4] broad-spectrum antibiotics[5-9] and prolonged use of corticosteroids.[7]

recent evidence establishes high rate of microbiological and clinical cure with AVC.[9-11]

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Dosage: One applicatorful or one suppository intravaginally once or twice daily.

Supplied: Cream — Four-ounce tube with or without applicator. Suppositories — Box of 12 with applicator.

References: 1. Gardner, H. L.: J. Miss. M.A. 8:529, 1967. 2. Porter, P. S., and Lyle, J. S.: Arch. Dermat. 93:402, 1966. 3. Walsh, H.; Hildebrandt, R. J., and Prystowsky, H.: Am. J. Obst. & Gynec. 93:904, 1965. 4. Vaginitis and the Pill: J.A.M.A. 196:731, 1966. 5. Guerriero, W. F.: South. M.J. 56:390, 1963. 6. Seelig, M. S.: Am. J. Med. 40:887, 1966. 7. To-day's Drugs, New York, Grune & Stratton, Inc., 1965, p. 316. 8. Gray, L. A., and Barnes, M. L.: Am. J. Obst. & Gynec. 92:125, 1965. 9. Salerno, L. J.; Ortiz, G., and Turkel, V.: Vaginitis: A Diagnostic and Therapeutic Approach, Scientific Exhibit, presented at the 115th Annual A.M.A. Convention, Chicago, Illinois, June 1966. 10. Walsh, J. C.; Sheffery, J. B., and Wilson, T. A.: Med. Ann. D.C. 37:358, 1968. 11. Nugent, F. B., and Myers, J. E.: Pennsylvania Med. 69:44, 1966.

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Dermatology

Cutaneous Biopsy

The cutaneous biopsy is often of great help in either establishing or confirming a diagnosis. Its use is not limited to potentially malignant skin lesions; it also may be of considerable help in diagnosing various skin diseases of diverse causes. Unlike biopsies from other organs, the skin biopsy specimen is easily and quickly removed in the office with a minimum of discomfort to the patient. Rarely is it necessary to excise with the scalpel. The necessary equipment is present in the office of most practitioners. Local anesthesia may be achieved easily by lidocaine (Xylocaine®). However, if the patient is allergic to this type of drug, satisfactory local anesthesia may be achieved with ethyl chloride spray or an antihistamine (intradermal).

Obtaining the specimen is greatly facilitated by the use of a skin biopsy punch which resembles a cookie cutter and is used in much the same manner (Figure). The instrument comes with circular blades of various diameters, probably the most practical being the 4 or 5-mm size. On the face it may be best to use the 2 or 3-mm punch. With these sizes scarring is generally inconsequential. However, it is not necessary to use this instrument in order to obtain a suitable specimen. A fine iris scissors and small single toothed forceps can be used very nicely in performing a small cutaneous biopsy. Circumscribed tumors (verrucae, seborrheic and actinic keratoses) can be re-

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Figure

moved with facility by curettage. If the biopsy site is not on a conspicuous location, suturing is usually not necessary; pressure or light electrocautery suffices to produce hemostasis in most instances, and healing is rapid.

Fixation of the specimen may be achieved with 10 percent formalin (4 percent aqueous solution of formaldehyde). It is best to allow the specimen to remain in the formalin at room temperature for six hours before shipping, especially if the weather is cold. In winter, if the specimen is to be mailed, 70 to 90 percent ethyl alcohol may be used as the fixative. Both formalin and alcohol have the disadvantage that fat is lost during fixation. The amount of fixative should approximate 20 times the specimen by volume.

The site from which the specimen is taken is important in getting the most information. Selecting a characteristic lesion from a commonly involved location is desirable. Depth is also important; if the disease has no induration, a specimen including most of the dermis is usually adequate. However, if a deeper process is clinically evident, such as a panniculitis* or nodular lesions of the lower extremities, then subcutaneous tissue should be included. This latter type of biopsy usually requires scalpel excision with sutures.

Timing can be important in performing the skin biopsy. For example, in vesiculobullous diseases early unruptured (not older than 24 to 48 hours) lesions taken out intact usually give the most information. If there are stages in the evolution of an eruption, it is best to choose a well developed lesion or two lesions of different stages. Also, if the condition has multiform characteristics, the physician may have to remove several specimens in order to gain the information he desires. This also is true in large ulcers where one wishes to exclude carcinoma by taking several specimens from indurated sites at the periphery.

When submitting the specimen it is important to include: the patient's name, age, sex, site of the biopsy, duration of the eruption or lesion, brief clinical description, and diagnostic possibilities. When sending the specimen to a general pathologic laboratory the physician should be sure the laboratory is willing to accept and process small cutaneous specimens. Many non-dermatologic laboratories are geared for larger surgical specimens, a routine which may cause excessive artifactual change in 2 to 6-mm sections.

The cutaneous biopsy is most useful in the identification of cutaneous cancer of various types, precancerous lesions, and a number of cutaneous diseases whose histopathology is characteristic. Even when not diagnostic, the cutaneous biopsy may be very helpful in differentiating other conditions whose pathology is characteristic. Other areas where the biopsy is helpful include bacterial and mycological infections where special stains may identify the organisms. In metabolic and other systemic disorders the skin is frequently involved, and here histochemical techniques as well as histopathology may help in arriving at a diagnosis. Biopsy does not always give a definite diagnosis; however, its use should be encouraged, for the information obtained may be of great help in the management of many dermatologic problems.

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*See Test Your Word Score Page 1637.

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An educated people is easily governed.—Frederick the Great.

Grand Rounds

Hypercalcemia Associated with Non-Parathyroid Tumors

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Case Report

The patient, a 71-year-old white male, had enjoyed generally good health until six months prior to admission, when he had an insidious onset of hoarseness, cough and chest pain. He was noted to have a right vocal cord paralysis at that time, but he refused further evaluation. He complained of weakness and difficulty swallowing during the five weeks prior to admission. He had also noted an enlarging mass in his neck.

On examination he was lethargic, with a hoarse voice, mild tachypnea, and a productive cough. There was a slightly tender, hard, fixed, three-centimeter paratracheal mass in the right suprasternal area, which was displacing the trachea markedly toward the left and appeared to extend into the superior mediastinum. There were findings of right lower lobe consolidation and guaiac-positive stool. He was noted to have hypoactive reflexes.

A chest roentgenogram showed a right lower lobe infiltrate with effusion. An electrocardiogram was normal with a QT interval of 0.38 seconds; Hgb. 13.8 Gm., WBC 12,000/mm^3, BUN 17 mg.%; albumin 2.8 Gm.%, alkaline phosphatase 12 K-AU., calcium 13.8 mg.%, phosphorus 2.9 mg.%. A sputum culture grew a mixture of gram-positive organisms.

The patient received intravenous antibiotics and fluids, as he could not maintain his hydration orally. A bone survey was negative, BSP retention 15% at 45 minutes. Urine: calcium 424 mg. in 24 hours, phosphorus 412 mg. in 24 hours, creatine clearance 30 cc/min. (Calcium free diet). PBI and T_3 were normal.

The patient was becoming more obtunded with a rising serum calcium (Figure), and further workup was interrupted on his fifth hospital day by the necessity to treat his hypercalcemia. He received approximately sixty mEq. PO_4 (as $K_2HPO_4 + KH_2PO_4$) intravenously over a twelve-hour period and during this procedure developed an antero-septal myocardial infarction. He convalesced with only mild congestive heart failure and became more alert after the lowering of serum calcium; but his pulmonary infection failed to clear and he developed progressive airway obstruction necessitating tracheostomy. An open biopsy of the cervical mass was obtained and revealed squamous cell carcinoma. He continued to deteriorate, developed elevated BUN and phosphorus terminally and expired on his thirty-fifth hospital day.

A squamous cell carcinoma of the distal esophagus was found at autopsy, with metastases to the thyroid, heart, adrenal, pleura, mediastinal lymph nodes, liver, and thoracic spine. Also noted were an antero-septal myocardial infarct, and a calcified granuloma of the right lung.

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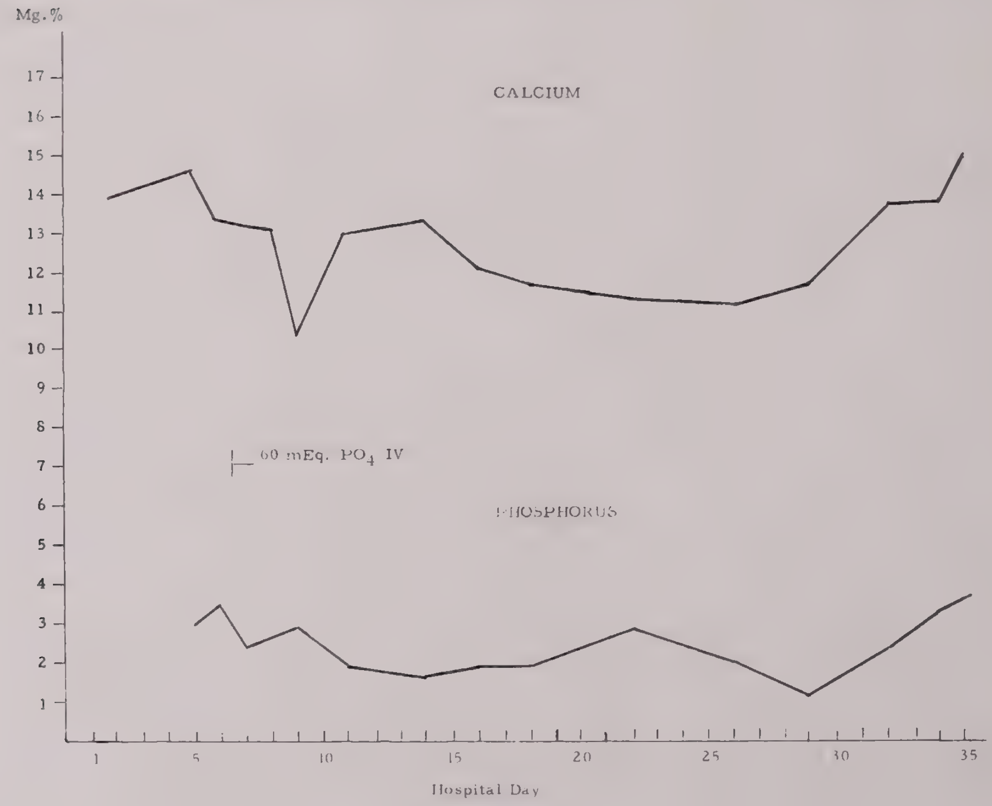
*Presented as a Medical Grand Rounds at Hennepin County General Hospital, March 18, 1969.

History

Hypercalcemia is a disorder that causes significant morbidity and may in some instances prove fatal. A number of disease states require consideration when a patient is found with an elevated serum calcium. Little enlargement has been made upon a summary credited to Albright in 1941[1]: Laboratory error, primary hyperparathyroidism, hyperthyroidism, immobilization (especially with Paget's disease or fractures), vitamin D intoxication, milk alkali syndrome, and neoplasm with skeletal lesions. Hypercalcemia associated with non-parathyroid neoplasm with no skeletal lesions has more recently been reported.

Gutman,[2] in 1936, described a man who had bronchogenic carcinoma with elevated serum calcium and low serum phosphate. He noted normal parathyroid glands and the absence of skeletal lesions at necropsy. In 1941, Albright[3] reported a similar case and was the first to postulate the production of parathyroid hormone by a non-parathyroid tumor. Connor, Howard and Thomas,[4] in 1956, reported two patients who reverted to normal calcium levels following removal of a lung tumor. Finally, in 1964, Tashjian et al.[5] identified a parathyroid hormone-like substance in six non-parathyroid tumors associated with hypercalcemia.

Hypercalcemia occurs with sufficient frequency to be considered in any patient with known cancer. Woodward[6] reported that 9% of 699 patients having a variety of malignancies and skeletal metastases exhibited hypercalcemia at some point during their disease. Metastatic bone disease or myeloma and non-metastatic malignant tumors accounted for 55% and 15% respectively of all elevated serum calcium determinations found at the University Hos-



Figure

pitals of Cleveland from 1961 to 1965.[7] Carey[8] studied 100 consecutive male patients with the tissue diagnosis of bronchogenic carcinoma. Eight were noted to have serum calcium greater than 12. Six had no clinical evidence for bone metastases and negative bone survey roentgenograms. All had "normal parathyroid glands" at post-mortem examination, and no other cause of hypercalcemia was found. While malignancy with skeletal metastases is known to have a high incidence of hypercalcemia, of patients with known cancer and hypercalcemia, 14-20% will have no demonstrable skeletal lesion.[9]

Etiology

No single explanation for these observations is possible. Osteolytic lesions in bone are felt to mobilize calcium at a rate faster than it can be excreted by the kidneys; but this cannot explain the hypercalcemia sometimes occurring with osteoblastic lesions. An early postulation was elaboration by the tumor of a calcium-binding substance, i.e., a globulin or lipoprotein similar to that found in hens with "normal" hypercalcemia during egg laying. Such a substance has not been found; and in patients studied, elevated serum calcium is found to be diffusable and normally ionized.[10]

Parathyroid Hormone

The presence of hypercalcemia, hypophosphatemia and elevated alkaline phosphatase strongly suggests the possibility of excess parathyroid hormone, presumably caused by excess stimulation of endogenous parathyroid hormone production or excess tumor production of parathyroid hormone (or parathyroid hormone-like substance). Sporadic cases appear with hyperplasia of parathyroid glands in association with hypercalcemia and malignancy; however, no known trophic hormone has ever been demonstrated in parathyroid regulation. Ionized serum calcium is accepted as the agent active in negative feedback in parathyroid hormone regulation.

As previously mentioned, Tashjian, Levin and Munsen,[5] using a very sensitive quantitative complement fixation reaction, have detected an antigen reacting with anti-parathyroid hormone in six tumors from patients with the hypercalcemia syndrome. The tumors originated from kidney, lung, pancreas, and colon without evidence of bone lesions. Extracts of non-tumor tissue from the same patients and similar tumors from patients without hypercalcemia were serologically negative. This assay method is several hundred times more sensitive than the previously used bio-assay and, in fact, detected an increase in circulating parathyroid hormone in one patient. Extracts from three of these tumors produced a small rise in serum calcium in parathyroidectomized rats. The evidence, therefore, seems irrefutable that at least some tumors are capable of secreting excess parathyroid hormone (or parathyroid-like hormone). Hypernephroma and bronchogenic carcinoma have accounted for approximately 60% of the reported cases in this category, so that they are by no means confined to an entodermal origin.

Vitamin D

Parathyroid hormone secretion will not explain all such cases of hypercalcemia, as immunoassay has been negative on numerous occasions. Localized carcinoma of the breast is strikingly absent from series with detectable parathyroid hormone. Gordon[11] et al. reported 20 of 80 cases of carcinoma of the breast to have hypercalcemia with normal bone surveys. These cases had hyperphosphatemia and normal renal tubular reabsorption of phosphate. This, together with the frequent response to cortisone, led Gordon to postulate the secretion of a vitamin D-like substance rather than parathyroid hormone. He subsequently was able to detect an osteolytic sterol in eleven of twelve breast cancers removed at surgery. This substance significantly increased urinary calcium in parathyroidectomized rats and was identified by thin-layer chromatography to be very closely related to 7-dehydrocholesterol (provitamin D_3). The osteolytic activity of this sterol probably accounts for the rise in serum calcium in carcinoma of the breast. These twelve patients had normal serum calcium determinations, suggesting that the body's efficient homeostatic mechanisms prevented hypercalcemia.

Conclusion

Elevated serum calcium, sometimes to life-threatening proportions, may coexist with malignant disease. While usually secondary to skeletal metastasis, it may occur with localized disease by production of a parathyroid hormone-like substance, a vitamin D-like substance, or by yet unidentified substances.

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It's the Law

Misfilling of Prescription for "The Pill"

The patient had been given a prescription for Norinyl, an oral birth control pill, by her physician. The prescription was mistakenly filled with Nardil, a mild tranquilizer. The patient took the pills furnished and in due time gave birth to a normal healthy boy.

The patient and her husband sought to recover as damages the cost of confinement, the patient's loss of earnings and support of the child until he was 21.

The court ruled that damages could not be awarded for the result of a natural conjugal act of husband and wife. The court ruled that any public policy that may exist favoring planned parenthood is outweighed by the public policy requiring the responsibility of parenthood to be borne by the parents.

Troppo v. Scarf, Cir. Ct., Wayne Co., Docket No. Civil Action 53523 (Michigan, March 24, 1969). The Citation 19:3, May 15, 1969.

Safety

He tried to cross the railroad track
Before the rushing train;
They put the pieces in a sack,
But couldn't find a brain.

Wall Street Journal

Laboratory Letter

"Normal Ranges" and Aging

> *"And so from hour to hour we ripe and ripe,*
> *And then from hour to hour we rot and rot,*
> *And thereby hangs a tale."*
>
> William Shakespeare, As You Like It, II, vii

To begin a letter about a scientific matter with a quote from Shakespeare may strike you as unorthodox. Perhaps so. But Shakespeare clearly saw what most "normal range" finders seem to have forgotten: as we age, we change. Before puberty, our metabolism and our body mature. Later, our hair grays, our vision dims, our skin wrinkles, and our walk slows. Or, if you want to be scientific, cardiac output and conduction velocity fall, renal plasma flow and glomerular filtration rate drop off, and vital capacity and basal metabolism rate gently, but relentlessly, decrease.

Why then shouldn't "normal ranges," which indirectly measure metabolism and body composition, change? We believe they do. Many ranges shift with age, depending partly on the sex of the subject tested; and clinicians who blindly accept a fixed normal range and disregard the patient's age and sex are going to make mistakes.

As far back as 1938, Rockefeller Institute investigators showed that BUNs climb in "healthy men"[1]; Keyes and his group at the University of Minnesota demonstrated in 1950 that cholesterol ranges fluctuate in men and women[2]; a couple of Cincinnati workers disclosed that calcium levels drift down with age[3]; and, just last year, a group at the University of Missouri used a computer to show that "normal ranges" for many tests shift with advancing age.[4]

All of which supports a recent study of our own. We took data from 6300 chemistry graphs (done on the Sequential Multiple Analyzer 12/30), punched the numbers on IBM cards, and ran the cards through a computer. The computer displayed frequency distribution patterns for the 12 tests for each age and sex for each decade. And then, instructed by a program that we will describe in detail in a later paper, we calculated the probable "normal range" for each group of patients. We list below those tests in which age and sex seemed to make a difference. You may find this data useful, as we have, in interpreting chemistry graphs.

Age	Cholesterol	Calcium	In. Phos.	Albumin	T. Protein	Uric Acid	BUN	Glucose
20-29M	110-215	8.8-10.7	2.3-5.1	3.1-4.7	6.1-7.8	3.2-8.5	7-18	70-115
W	85-250	8.6-10.5	2.3-4.8	2.9-4.5	6.1-7.6	2.2-6.6	5-16	70-105
30-39M	120-250	9.0-10.4	2.6-4.2	3.4-4.6	6.2-7.8	3.7-8.4	7-20	75-115
F	125-265	8.5-10.1	2.4-4.3	2.6-4.5	5.5-7.8	2.1-6.3	6-15	75-105
40-49M	135-305	8.8-10.4	2.2-4.2	3.3-4.6	6.1-7.7	3.2-8.4	7-20	80-110
F	135-265	8.3-10.4	2.4-4.3	2.7-4.4	5.7-7.8	1.5-6.6	5-17	75-105
50-59M	150-310	8.8-10.3	2.3-4.0	3.0-4.4	5.9-7.8	3.1-8.8	6-23	80-110
F	140-305	8.6-10.4	2.5-4.5	2.8-4.5	5.7-7.8	2.0-7.3	6-20	75-110
60-69M	145-325	8.6-10.2	2.2-4.0	2.7-4.5	5.7-7.7	2.8-8.9	7-25	80-120
F	150-325	8.6-10.3	2.5-4.5	2.6-4.4	5.5-7.8	1.8-7.7	5-23	80-110
70-79M	120-285	8.3-10.2	2.0-4.1	2.3-4.3	5.4-7.7	2.5-9.4	6-28	80-120
F	120-320	8.4-10.2	2.4-4.3	2.3-4.4	5.3-7.8	1.9-8.0	5-25	80-115
80-89M	100-250	8.1-10.1	2.2-3.9	2.1-4.1	5.5-7.7	2.8-9.1	7-31	75-125
F	120-265	8.2-10.2	2.4-4.1	2.1-4.1	5.1-7.6	1.5-8.1	5-29	75-120

References may be secured from the author.

Richard L. Reece, M.D.
Minneapolis, Minnesota

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Continued to page 1692

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effect on lactation may occur.

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Clinical Review

Tumors in Infancy and Childhood*

Advances in the diagnosis and treatment of tumors in infancy and childhood have been many during the past decade. In this review, some basic aspects of tumors in infancy and childhood will be considered, but detailed characteristics of individual tumors will not be discussed. The purpose is to promote overall knowledge and understanding of childhood tumors and aid in meeting the challenge that now confronts all those working in the field of pediatrics.

Cancer kills more infants and children than does almost any other disease, including tuberculosis, heart disease, and poliomyelitis.[1] It is fourth in causes of death in the preschool years and second in the age group five through 14 years, being exceeded in the latter group only by accidents.[1] Some of the most rapidly fatal cancers, such as acute leukemia, occur in infants, and some of the most disfiguring tumors occur in children. In 1956, almost 4,000 infants and children in the United States died from cancer, representing 9% of all deaths in that age group.[1] In a recent survey, more than 1% of all patients entering a children's hospital had malignant tumors.[2]

The first authentic account of tumors in children was that of Wardrop in 1809, who mentioned 20 malignant tumors of the eye in children. In 1846, Walshe reported a tumor of the dura mater in a child; he also collected reports of 44 cancers of the cerebral meninges and cranium.

The first comprehensive survey of the literature on childhood cancer was that of Duzan, who found 231 cancers reported between 1832 and 1875. A few years later, Picot reported an additional 242 cancers in children. This was followed by a review by d'Espine and Picot in 1900, giving a total of 640 childhood cancers.

Until the 1930s, reports continued to be sporadic. Significant contributions were those of Steffen (1905), Williams (1908), Wright (1910), Warthin (1915), Schultze (1926), Raymond (1929), and Helmholz (1931).

After 1930 the number and scope of clinical and experimental reports on the various aspects of cancer in children increased rapidly. Today there is a vast literature in a great variety of medical journals.[3]

General Appraisal

Childhood cancer is most often observed in the first five years of life, probably reflecting the embryonal nature of certain of the more common tumors encountered in this period. They may be present at birth or may arise postnatally from cells that have not attained complete maturation. The comprehensive review of congenital malignant neoplasms by Wells[4] in 1940 remains the classic to that date. Vinik and Altman[5] in 1966 reported congenital fibrosarcoma, neuroblastoma, reticulum cell sarcoma, undifferentiated sarcoma, and malignant histiocytosis. Congenital cancers may affect the kidneys, eyes, adrenals, testes, ovaries, and many other soft tissues. Rudimentary organs are also common sites.

A pregnant woman with far-advanced neoplastic disease, especially malignant melanoma, may transmit the process to her offspring.[6] Reports indicate that infants have died of a malignant tumor similar to that of the mother.[7] Cyst, angioma, mole, and chorioepithelioma are the commonest types of fetal tumor.[3]

Sites of origin of tumors in children differ from those of adults. Common epithelial tumors in adults (carcinoma of the skin, stomach, breast, and uterus) are rare in early life. The six body sites most often involved in the child are the intracranial cavity, eyes and orbit, bones, hematopoietic sites, soft somatic tissues, and retroperitoneal region.

The terms "malignant" and "benign" as applied to tumors may be misleading. Because of their location, histologically benign tumors of the central nervous system are associated with high mortality rates. Wilms's tumor and even neuroblastomas are often initially encapsulated.

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*See editorial page 1629.

Benign Tumors

These are far more common in early life than are malignant ones, and many of them represent hamartomas rather than true neoplasms. Hamartomas are tumor-like, non-neoplastic malformations characterized by localized overgrowth of one or more tissues indigenous to the site in which they arise, for example, angiomas. Benign tumors found in adults, such as uterine polyps and fibroids, adenomas of the thyroid and adrenal glands, adenomatous hyperplasia of the prostate, fibroadenomas of the breast, and papillomas of the urinary bladder are rare in early life.

In a series of 1,872 benign tumors in children, those of mesodermal origin far outnumbered those of any other origin; 1,525 (81.5%) were of mesodermal origin (vascular 769, soft parts 563, bone 193), 59 ectodermal, 15 endodermal, six mixed, and 267 of miscellaneous origin.[3]

Malignant Tumors

Sarcoma is far more common than carcinoma in children. The reverse is true in adults. The location and the histologic type of malignant lesions have varied with the years and from clinic to clinic. Of 1,418 malignant tumors reported by Dargeon,[3] 534 (37.7%) were lymphomas and leukemias, 383 (27%) sarcomas (osseous and somatic), 105 (7.4%) carcinomas, and 396 (27.9%) others (171 neuroblastomas, 93 Wilms's tumors, 57 retinoblastomas, 14 central nervous system tumors, and 61 miscellaneous tumors).

Handy and Goldberg[8] reported that malignant neoplastic conditions in patients less than 15 years old occur in decreasing order of frequency as follows: leukemias, brain tumors, renal and adrenal tumors, lymphosarcomas, tumors of the digestive system, sarcomas of soft tissue, and bone tumors.

Of 2,230 autopsy protocols of children less than 15 years old seen at the Mayo Clinic for the 16-year period 1950 through 1965, 204 concerned patients with malignant tumors, distributed as follows: lymphomas and leukemias 97, (leukemias 83, lymphomas 14), intracranial tumors 66, sarcomas 17, renal and adrenal tumors 11, and miscellaneous tumors 13.

Leukemia

Leukemia, a fatal disease in children, is characterized by uncontrolled proliferation of leukocytes and their precursors. It is usually acute and of relatively short duration in children. It occurs more often in the first five years of life, with a second peak at eight to nine years. The type of cells predominantly involved in leukemia offers a basis for classification. In childhood, however, the predominating cell is often so undifferentiated morphologically (stem cell) that a specific diagnosis according to origin of the cell cannot be made.

The symptoms of leukemia are due to (1) hypermetabolism associated with rapid growth and destruction of leukemic tissue, (2) bone marrow dysfunction, and (3) disturbances of organs involved in leukemic proliferation. The spleen, liver, and kidneys are usually enlarged. Enlargement of lymph nodes is generally not marked, but mediastinal and abdominal nodes may be extensively enlarged.

Chronic leukemia is uncommon in children. It is almost always myelocytic in origin, and usually has its onset after the age of eight years. Congenital leukemia, present at birth or developing shortly thereafter, is always of the acute type.

Tumors of the Head and Neck

Various tumors may occur in the head and neck of children. Of 233 such tumors reported by Dargeon,[3] 68 were of the eye and orbit (56 retinoblastomas), 59 of the soft parts (21 neuroblastomas, 12 rhabdomyosarcomas), 25 of the nasopharynx, 19 of the thyroid, 11 of the tonsil, 10 of the skin, 10 of the brain and membranes, seven of the skull, six of the nasal cavity, four of the paranasal sinuses, two of the salivary glands, two of the palate, three of the mastoid and ear, six of the lip, gingiva, and cheek, and one rhabdomyosarcoma of the tongue.

Eye

Retinoblastoma is the most common tumor of the eye. It has a marked hereditary proclivity and may be present at birth, but the average age at discovery is about two years. Both eyes are involved in one third of the patients afflicted. In advanced cases the tumor produces a white reflex in the pupil and may break through the globe and extend to the surrounding structures. Reese[9] states that more than half the offspring of a parent who survives the disease develop retinoblastoma. Healthy parents who have one child with retinoblastoma only rarely have a second afflicted child, and such parents should not be discouraged from having more children.

Most tumors of the orbital tissue are mesenchymal in origin. Proptosis is usually an early symptom.

Nasopharynx

Angiomas and polyps often occur in the nasopharynx. Juvenile nasopharyngeal angiofibroma occurs almost entirely in males, generally between ages 10 and 20 years. Nasal obstruction and epistaxis are the usual clinical manifestations.

Teratomas may arise at the base of the skull, in the roof of the pharynx, or in the palate, and may project into the mouth, nose, or cranial cavity. A chordoma of the base of the skull may project into the nasopharynx or manifest itself initially as an intracranial tumor.

Tumors of the salivary glands are uncommon, but chiefly affect the parotid. Hemangioma is the most common salivary tumor in early life, and mucoepidermoid carcinoma is the most common malignant salivary tumor in children.

Tumors of the larynx are rare. Possible obstruction of the airway by these lesions may cause a critical situation. Angiomas, polyps, and fibromas may occur in the larynx.

The Neck

Teratomas, lymphangiomas, lymphomas, neuroblastomas, and rhabdomyosarcomas occur in the neck. A thyroglossal duct cyst in the midline, a branchial cleft cyst along the lateral aspect of the neck, and an aberrant salivary, thyroid, parathyroid, or thymic tissue may present as a mass in the neck.

Thyroid

Benign tumors of the thyroid are rare. Thyroid carcinoma may be present at birth; the average age at occurrence is about nine years. Approximately 65% occur in girls.[10] Papillary carcinoma accounts for the largest number. An asymptomatic nodule in one lobe of the thyroid is the classic clinical feature. The incidence of cervical metastasis when these patients are first seen has been reported to be as high as 70%.[11] The lungs are the most common distant site for metastasis. Every thyroid nodule identified in a child should be removed and examined, since the incidence of carcinoma is about 70%.[6] In 1961, Winship and Rosvoll[12] reported that 38% of 562 recorded thyroid carcinomas in children were associated with a history of previous therapeutic irradiation of the neck.

Adenomas of the parathyroid glands, which may be aberrant in the region from the mandible to the mediastinum, are rare in children.

Tumors of the Brain and Spinal Cord

These tumors are rare in infancy, but the incidence increases rapidly to a peak at five to six years of age. There is no general predilection for race or sex. Sixty to 70% of brain tumors in children are beneath the tentorium cerebri,[6] the reverse of the pattern in the adult. Of the supratentorial tumors, more than half are in the midline. About 75% of intracranial tumors in childhood are gliomas, of which two thirds are astrocytomas and medulloblastomas. Ependymomas, brain-stem gliomas, and gliomas of the hemispheres constitute an additional 15%, and the remainder are craniopharyngiomas, meningiomas, sarcomas, pituitary adenomas, hamartomas, hemangiomas, and dermoids. The acoustic neuroma, meningioma, and pituitary adenoma of adult life are rare, as are metastases from non-cerebral neoplasms.

Of 1,369 reported intracranial tumors of infancy and childhood,[3] 369 were astrocytomas, 283 medulloblastomas, 143 ependymomas, 81 craniopharyngiomas, and 493 miscellaneous tumors.

The general symptoms of brain tumor in childhood are caused by increased intracranial pressure. Vomiting usually occurs in the morning, often without nausea; only late in the course does projectile vomiting appear. Headache occurs in 70% of cases, more frequent at night or when the child arises from sleep. Enlargement of the head occurs most often in children less than four years old. Convulsions, mental change, gait disturbance, and diplopia are other symptoms.

Tumors of the spinal cord rarely occur in children. They affect the sexes equally. Ependymomas are the most common type. Austin[13] reported 30 spinal cord tumors in children in a series of 409 spinal cord tumors representing all ages and seen over a period of 25 years in a neurologic clinic.

Tumors of the Thorax

Tumors of the breast and of the chest wall, benign or malignant, are uncommon in children,[1,14,15] but malignant ones are more common than benign ones. Sarcomas make up the principal group of these tumors.[11,16,17]

Lung

Pulmonary metastasis from Wilms's tumor, neuroblastoma (rare), or osteogenic sarcoma is more common than primary malignancy of the lung. There have been some rare reports of various types of sarcoma and epithelial malignant tumors of the lung.[18-20] Bronchial adenoma is occasionally seen, and Ward, Bradshaw, and Prince[21] in 1954 found reports of eight cases in children and added a ninth.

Heart

Tumors of the heart are rare. Rhabdomyomas show a definite predilection for infants and children. Myxomas are the most common primary tumors of the heart, and sarcomas the second.[1]

Mediastinum

Cysts and tumors of the mediastinum are not rare. The clinical manifestations of these masses are essentially those of expanding, space-occupying lesions and reflect their location. Symptoms most often encountered are chest pain, cough, respiratory distress, hemoptysis, dyspnea, and weight loss. A number of these cysts and tumors, even when large, are asymptomatic and show only incidentally on chest roentgenograms. The distribution of various types of mediastinal cysts and neoplasms seen in a combined series from the Mayo Clinic (56 cases)[22,23] and the Johns Hopkins Hospital (25 cases)[24] is as follows: neurogenic tumors 37%, teratomatous tumors 25%, cysts of foregut origin 16%, hemangiomas 6%, cystic hygromas 5%, anaplastic neoplasms 5%, miscellaneous tumors 6%. The neurogenic tumors, occurring entirely in the posterior mediastinum, make up the largest group, and the teratomas and dermoids in the anterior mediastinum the second largest.

The tumors and cysts occurring in the different parts of the mediastinum and listed in descending order of frequency are as follows: (1) superior mediastinum: goiter, bronchogenic cyst, parathyroid adenoma, myxoma, lymphoma, and neurilemmoma; (2) anterior mediastinum: thymoma, teratoma, goiter, parathyroid adenoma, lymphoma, lipoma, fibroma, angioma, chondroma, thymic cyst, and rhabdomyosarcoma; (3) middle mediastinum: bronchogenic cyst, lymphoma, and pericardial cyst; and (4) posterior mediastinum: ganglioneuroma, neuroblastoma, neurilemmoma, neurofibroma, neurofibrosarcoma, ganglioneuroblastoma, lymphoma, gastroenteric cyst, chondroma, myxoma, goiter, fibrosarcoma, and meningocele.

Since some mediastinal tumors have malignant potentialities, and most others sooner or later cause symptoms by virtue of their location, all such cysts or tumors should be removed when discovered even if they have not yet produced symptoms.

Abdominal Tumors

The discovery of an abdominal mass in a child presents a challenging problem. More than half of these masses are nonsurgical; the remainder (40 to 45%) are of surgical importance. Hydronephrosis accounts for a little more than half of the surgical conditions. The remainder are neoplastic and must be considered malignant until proved otherwise.

In a series of 653 palpable abdominal masses in infants and children,[25] 372 (57%) represented medical conditions and 281 (43%) represented surgical conditions. The medical conditions were leukemia (209 cases), hepatosplenomegaly of unknown etiology (67 cases), Banti's syndrome and splenomegaly (49 cases), Hodgkin's disease (15 cases), and miscellaneous (32 cases). The surgical conditions were of genitourinary (49.5%) or of nongenitourinary (50.5%) origin. Genitourinary conditions were hydronephrosis (40.2%), Wilms's tumor (30.2%), cystic disease of the kidney (22.3%), and miscellaneous conditions (7.2%). The nongenitourinary conditions were intraperitoneal lesions (40.1%), neuroblastomas

(33.8%), primary retroperitoneal tumors (lymphoma, sarcoma) (20.4%), and miscellaneous conditions (5.6%).

Faced with an abdominal mass, one must first determine whether it is intraperitoneal or retroperitoneal. Shifting of the intraperitoneal mass can be felt and seen as it is pushed or as the patient is moved into different positions. Retroperitoneal masses, on the other hand, are fixed and are felt deep in the renal fossa. Malignant masses are hard; a hydronephrotic mass is usually soft. Appropriate roentgenographic examinations are essential to assess the nature and extent of the lesion.

About nine tenths of the retroperitoneal neoplasms are Wilms's tumors or neuroblastomas. Teratoma is the third most common type.[6]

Wilms's Tumor

Almost all renal tumors in infants and children are Wilms's tumor.[26-28] More than 90% of these tumors appear before the sixth year of life, the average age being three years. The tumor is bilateral in 4%, on the right in 44%, and on the left in 52%.[29,30] The sexes are almost equally affected, and familial occurrence is rare.[31-36] The primary clinical manifestation is an abdominal mass, present on physical examination in 90% and reported by the parents in 64%. It is careful examination by the physician that detects many of these tumors. Pain occurs in about 26% of cases, fever in 20%, vomiting in 16%, constipation in 6%, and diarrhea in 3%; hypertension may be encountered.[31,37,38] Metastatic lesions are present in 20 to 50% of patients on initial diagnosis and appear most commonly in the lung, then in the liver, and rarely in bone. Hematuria develops in 15 to 20% and is a grave prognostic sign. The presence and normality of the opposite kidney should be established by pyelography.

Management of patients with Wilms's tumor is still not standardized. It is universally agreed, however, that the best hope for permanent cure rests on excision of the tumor. Irradiation as the sole therapy gives poor results. The controversy hinges on the use of irradiation to augment surgical treatment. Recently dactinomycin (actinomycin D) has been reported as having had beneficial effects when given both preoperatively and postoperatively. Prognosis for the youngest children is much better than for older ones.[39,40]

Neuroblastoma

Although this tumor may originate anywhere along the sympathetic chain, 70% of neuroblastomas arise from the adrenal or upper abdominal sympathetic ganglia. It is the most common malignant neoplasm to be identified at birth, when metastatic lesions may already be present. There is no predilection for either sex or any race. Two thirds of these tumors originate on the left side[41] and 40% appear within the first year.[42] The peak incidence of admissions to the hospital is about age 1½ years. The presenting complaint is usually that of an abdominal mass. Pain, fever, anorexia, vomiting, weakness, and failure to gain weight —each or all may occur. A characteristic roentgenographic finding is calcification in the soft-tissue tumor. Pulmonary metastasis occurs in about 12% of cases and osseous metastasis in 35%.[43] Treatment is primarily surgical. The younger the child at the time of diagnosis the better the prognosis.

Tumors of the pancreas are extremely rare. Up to 1959, nine cases of adenocarcinoma of the pancreas had been reported.[44,45]

Metastatic neoplasms of the liver are more common than primary tumors in childhood. Most primary neoplasms are malignant.[6] These tumors must be considered in the differential diagnosis of a mass in the upper part of the abdomen. Up to 1958, 100 primary hepatic tumors in children had been reported.[46] In the newborn, hemangioendothelioma, solitary cyst, and cavernous hemangioma are the most common. Between birth and the age of two years, almost any benign or malignant tumor may occur in the liver. Beyond the age of two years, carcinoma, mesenchymoma, and solitary cyst are fairly common.[47]

Gastrointestinal Tract

Tumors of the gastrointestinal[48-56] tract may be asymptomatic or may be manifested by abdominal pain, intestinal obstruction (especially intussusception), hemorrhage, or rarely a palpable abdominal mass. Except for juvenile polyps, no tumor of the gastrointestinal tract can be considered common in children, but both benign and malignant neoplasms do occur.

Juvenile polyps have their peak incidence around four years of age. They are usually solitary and located in the rectum. There is no evidence that these polyps undergo malignant transformation.

Multiple familial polyposis is characterized by the presence of innumerable sessile and pedunculated tumors in the rectum and colon. If untreated, almost all patients with such tumors develop carcinoma. Treatment consists of total colectomy.

The polyps in Peutz-Jeghers syndrome are usually multiple and are located at several sites in the gastrointestinal tract, the small intestine being the site of predilection. The lesions are usually benign.

The polyps in multiple polyposis of the colon and rectum in Gardner's syndrome, which may not develop until adult life, are scattered and do not carpet the colonic mucosa. They have a striking tendency to malignant transformation.

Lymphoma is the most common malignant neoplasm of the gastrointestinal tract encountered in early life. The peak incidence is at three to eight years of age. Although usually arising in the small intestine, lymphomas may originate in the colon or even the stomach.

Carcinoma of the colon is rare in children. It may occur as a complication of multiple familial polyposis or of chronic ulcerative colitis. Rarely does it occur in the absence of known predisposing factors.

Carcinoid is seen in less than 0.2% of the appendices removed from children less than 14 years old.

Hemangioma of the intestine, teratoma of the stomach, and leiomyoma and leiomyosarcoma of the gastrointestinal tract are extremely rare.

Tumors of Bone

Various benign and malignant neoplasms of bone[57-71] have been described in children. Pain is common to most bone tumors that occur in children. Detecting local swelling and tenderness is important, but the roentgenographic appearance, although not pathognomonic, is more helpful in detecting the nature of the tumor. In a given patient the most accurate diagnosis is usually made by considering all aspects of the lesion: clinical history and signs, roentgenographic appearance, and especially pathologic findings. A roentgenographic survey of the other bones is necessary to determine whether the lesion in question is single or multiple.

Ewing's Tumor

The most common primary malignant tumors of bone are osteogenic sarcoma and Ewing's tumor, the majority of which occur between ages 10 and 25 years. Males are affected more often than females. Osteogenic sarcoma characteristically involves the metaphyseal end of a long bone, whereas Ewing's tumor involves the shaft. Osteogenic sarcoma is more common than Ewing's tumor.

Osteochondroma

Solitary osteochondroma is one of the most common of the benign osseous tumors. Bone cysts occur almost exclusively in the child and seldom develop after closure of epiphyses.

Lymphoma and leukemia frequently affect the osseous system in children. Lesions that may simulate plasma cell myeloma roentgenographically in the child are most likely due to reticuloendotheliosis.

Tumors in the skeleton may be metastatic from primary neoplasms known to occur in the child (neuroblastoma, Wilms's tumor, and retinoblastoma). Hence, the presence of such a skeletal tumor should lead one to search for the primary neoplasm.

Soft-Tissue Sarcomas of Infants and Children

Here the clinicopathologic studies[1,3,6,9,72-91] made by one of us (G.H.M.) will be summarized.

Material and Method

The soft-tissue sarcomas reported here occurred in 135 patients less than 16 years old who were seen at the Mayo Clinic in the 16-year period 1950 through 1965. The clinical records and autopsy protocols were reviewed and follow-up data on all survivors were obtained. Tissue sections were available for review in all cases. Tumors of the central nervous system, intracranial sarcomas, and malignant lymphomas are not included in the series.

Observations

Of the 135 patients, 67 were boys and 68 were girls. The mean age was 7.3 years. Ninety-two patients have died, 36 are living, and seven are lost to follow-up.

Eighty-one of the 135 patients received their initial treatment prior to January 1, 1961. Nineteen or 20.9% of these 81 patients are living five or more years after diagnosis.

Of the 11 histologic types of sarcoma encountered, rhabdomyosarcoma was the most common (75 cases), followed by sarcoma of undetermined histogenesis (27 cases), malignant synovioma (10 cases), juvenile fibrosarcoma (six cases), neurofibrosarcoma associated with von Recklinghausen's disease (five cases), leiomyosarcoma (three cases), malignant hemangiopericytoma (three cases), liposarcoma (two cases), dermatofibrosarcoma protuberans (two cases), malignant mixed mesenchymoma (one case), and extraosseous osteogenic sarcoma (one case).

The most common site of primary lesions was head and neck (51 cases), followed by the pelvis (28 cases), lower extremity (23 cases), upper extremity (18 cases), trunk (10 cases), and retroperitoneum (five cases).

The rhabdomyosarcomas were classified as embryonal (61 cases), embryonal with botryoid pattern (11 cases), embryonal with alveolar pattern (two cases), and pleomorphic (one case). The most common site of the primary tumor was the head and neck (38 cases); other sites were the pelvis (22 cases), extremities (nine cases), retroperitoneum (five cases), and chest wall (one case). Of the 75 patients, 60 have died and 15 are living. As of 1966, nine patients have lived five years or more and apparently are free of disease, four are living and free of disease after periods ranging from two months to three and a half years, and two are alive but have uncontrolled metastasis. Of the 51 traced patients treated prior to January 1961, seven (14%) lived five or more years after their initial treatment.

When practicable, ablative surgery appears to be the most effective treatment for rhabdomyosarcoma. When such treatment is not feasible, irradiation combined with chemotherapy and as wide a surgical removal as possible seems to be the best alternative for control of the primary lesion. The chemotherapeutic agent most frequently used in this series was dactinomycin.

General Clinical Aspects of Tumors in Childhood

The value of a complete history and a thorough physical examination in pediatrics is nowhere greater than in establishing the diagnosis of childhood tumors. The possibility of cancer must be included in the differential diagnosis of many children's diseases. The clinical manifestations of certain neoplasms in infants and children may be those of an acute infectious process with a few or none of the classic signs of malignancy encountered in adults. The child who shows significant differences, physically or mentally, from his fellows may have cancer. Any undiagnosed disorder of short or long duration could be due to cancer. Except for leukemia and tumors of the central nervous system, most malignant neoplasms in infants or children are manifested as an abnormal mass, which may quickly enlarge.

The first requisite of diagnosis is teamwork involving the clinician, the roentgenologist, the surgeon, and the pathologist. Every solid mass in an infant or a child should be regarded as a malignant neoplasm until proven otherwise.

Management

Needless palpation of a suspected neoplasm should be avoided. The mass should be removed as soon as consistent with adequate clinical evaluation and preparation for operation. Thus, there should be minimal delay, minimal handling, and a minimal number of studies. The word "malignant" does not always indicate a hopeless disease. Patients with certain neoplasms, notably neuroblastoma and Wilms's tumor, can sometimes be cured even in the presence of recognizable metastasis.

From a biologic as well as a sociologic standpoint, children are not simply "microadults." Their specific needs fully justify the establishment of special facilities for their care. The traditional therapeutic principle of treating the patient (and the family) as well as the disease also finds wide application in the treatment of tumors in children.

The cure of a cancer in a child is a particularly significant triumph, when one considers the long-term salvage. In the removal of tumors in childhood one thinks in terms of 70-year survival, rather than the five-year survival that is the mark of successful cancer therapy in adults. Observance of accepted principles should prevent a number of needless deaths from cancer in infants and children.

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20-91. May be secured from the author.

The Biopsy

1850-1900

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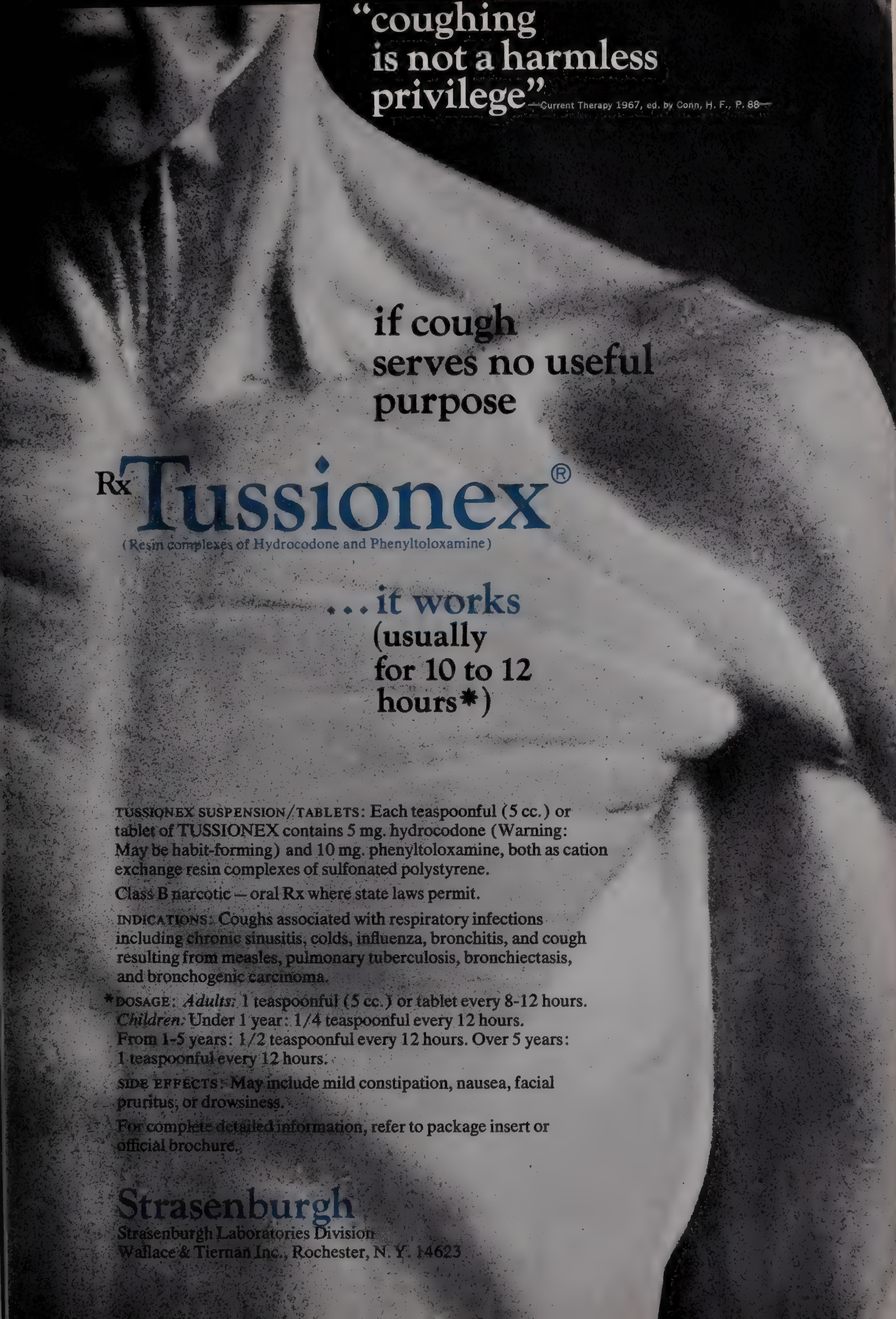
*The Patient's Progress, Edited by Felix Marti-Ibanez, 1962.

Editor's Note: I can visualize that argument between a couple of prima donnas, the surgeon and the pathologist. I guess I would have to agree with Virchow.

More than one cigar at a time is excessive smoking.—Mark Twain



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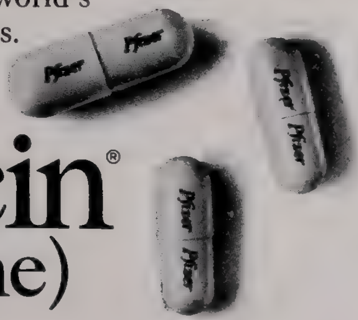

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Continued from page 1674

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Special Article

Splitting of the Atrial Sounds

DAVID GOLD, M.D.*
Minneapolis, Minnesota

THE ATRIAL SOUND (fourth heart sound, S4) is a low-pitched, low-intensity sound usually best heard at the cardiac apex with the patient in the left lateral decubitus position. Usually it blends with the first heart sound and thus, in combination with the mitral and tricuspid closure sounds, contributes to the "first-sound complex."[1,2]

Atrioventricular block is a clinical condition in which the atrial and ventricular contractions may occur sufficiently apart so that the atrial sound and the main part of the first heart sound can be heard separately.

The Cambridge Audio-Visual phono-cardiograph can be used in studying the characteristics of the atrial sound. The microphone is a bell-type of 5 cm. diameter. The frequency characteristics of the instrument are favorable for detecting low-pitched vibrations, and the oscilloscope permits the physician to observe the visual display of the vibrations as he hears the sounds. Finally, a magnetic tape recording may be made and the record replayed and examined at leisure.

Methods

Patients with either first-degree or complete A-V block were studied after auscultation with the conventional stethoscope suggested that the atrial sounds were audible. The patients' heart tones were recorded with the Cambridge Audio-Visual phonocardiograph. Often much patience was required in exploring the precordium in order to find the area where the atrial sound could be best heard. A simultaneous electrocardiogram was recorded on a separate machine.

Results

Thirty patients with varying degrees of A-V block were studied, most of whom demonstrated atrial sounds. Of special interest are four cases in which the atrial sounds during some cardiac cycles appeared to be split into two components. A photographic display of the phonocardiogram and the separate electrocardiogram of each of these patients is shown in Figures 1 to 4.

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*Mount Sinai Hospital.

Discussion

Splitting of the atrial sound could be demonstrated in four patients during some but not all cardiac cycles. The split was demonstrated best whenever the P-wave (and the atrial contraction) fell between ventricular contractions. There was no difference in clinical characteristics between patients with split atrial sounds and those with unsplit atrial sounds.

It is possible that in some patients the contraction of the right and left atria, in sequence, results in separate sounds that can be detected as a split atrial sound. In most clinical situations, however, the sounds associated with right and left atrial contractions are close together and are recorded as a single, fused atrial sound.

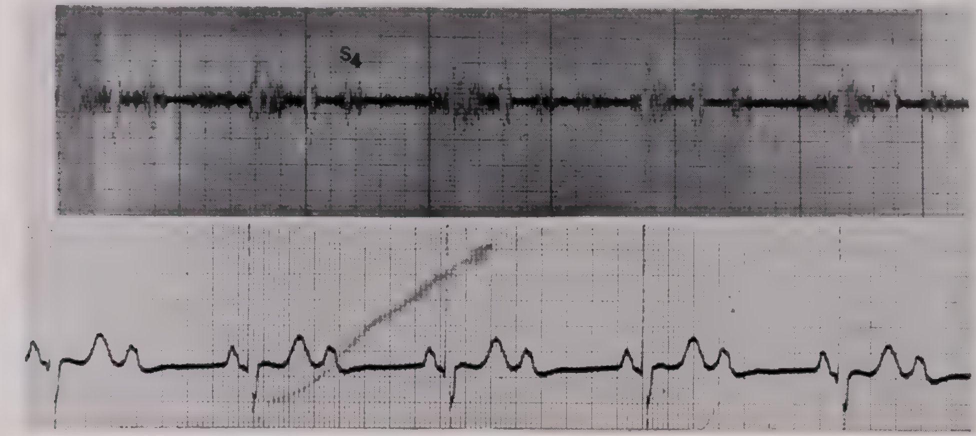

Figure 1

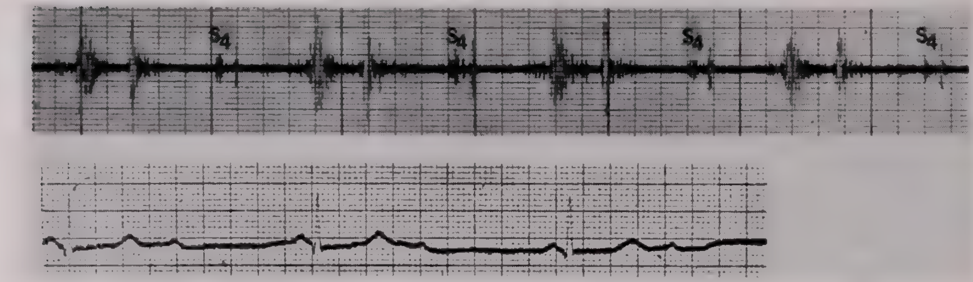

Figure 2

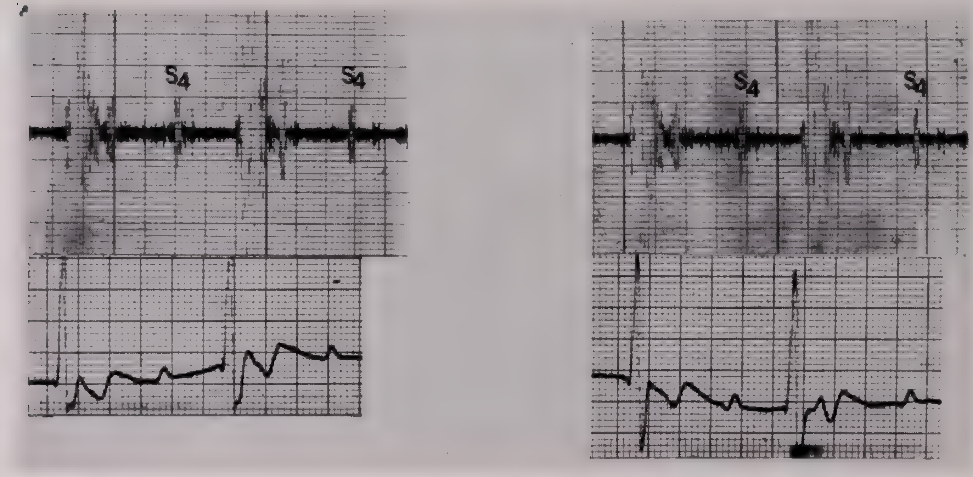

Figure 3

Several reports in the literature contain illustrations in which the atrial sounds appear to be split. Rytand's[3] "atrial murmur" may be a variant of a split atrial sound. Merrill, et al.[4] recorded "doubled" atrial sounds transmitted along the radial artery. Heyman[5] recorded atrial waves of a "double wave form" over the brachial and radial arteries. Butterworth[1b] has described split atrial sounds.

The phenomenon of the splitting of the atrial sound is demonstrable only under special conditions, such as A-V block, when the atrial sound is far enough removed from the ventricular sound so that it is not obliterated by the first and second heart sounds.

Inspection of the phonocardiographs shows that the two components of the split atrial sound have a slightly different configuration. A hypothesis may be suggested to explain this: The atrial contraction pumps blood into the ventricle and the ventricular wall bulges outward producing a "thud"—the atrial sound (fourth heart sound). This sequence occurs in the right and left ventricles. The wall of the right ventricle is thinner than that of the left ventricle; consequently the "thud" produced by the right ventricle produces a different phonocardiographic image than the "thud" produced by the left ventricle.

Conclusion

With the aid of an audio-visual phonocardiogram four patients with A-V blocks were found to exhibit splitting of the atrial sound. The mechanism of this splitting is discussed.

Case Summaries

Case 1: Age 79. Height 66 inches, weight 180 lbs. Blood pressure 250/100. Presenting symptom: Dyspnea, 2:1 to 3:1 A-V block. Treatment: Intravenous demand-type pacemaker.

Case 2: Age 71. Height 63 inches, weight 102 lbs. Blood pressure 130/80. Presenting symptom: Dizziness, 2:1 to 3:1 A-V block. Treatment: Intravenous pacemaker.

Case 3: Age 54. Height 68 inches, weight 150 lbs. Blood pressure 140/80. Presenting symptoms: Weakness, dizziness, First-degree A-V block.

Case 4: Age 88. Height 68 inches, weight 164 lbs. Blood pressure 120/80. Parkinsonism. First-degree A-V block.

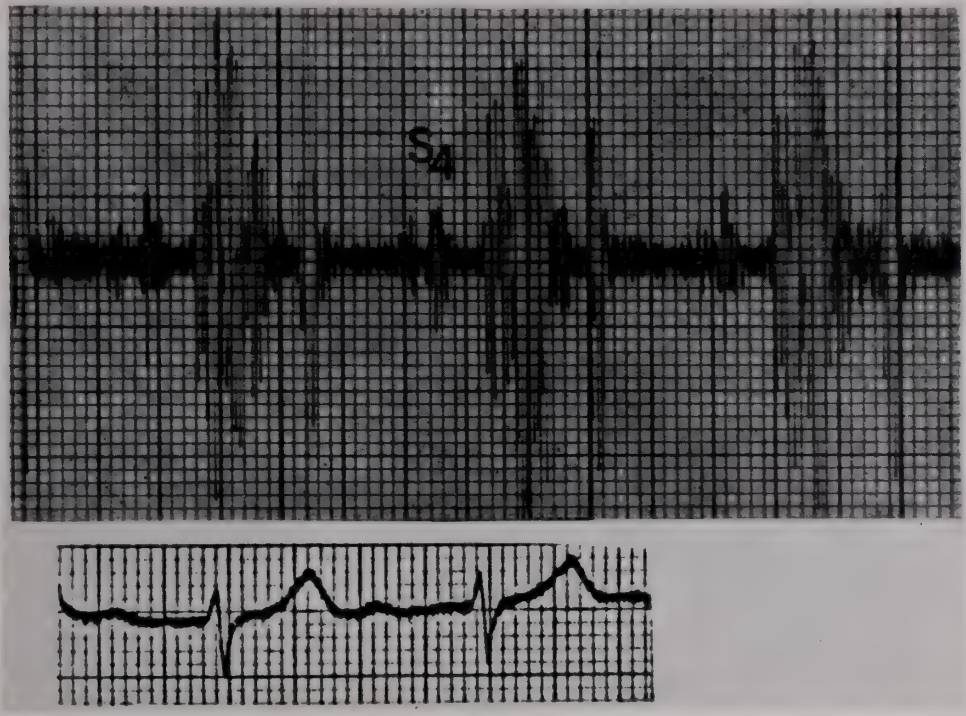

Figure 4

The atheist is a man who has no invisible means of support.—Lord Tweedsmuir

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References may be secured from the author.

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Tybatran (tybamate) has been useful in the control of agitation in the aged and in the alleviation of some of the adverse emotional accompaniments of senility.

Tybatran (tybamate) has been used with benefit in the treatment of depressive symptoms associated with anxiety and other symptoms of psychoneuroses. However, it is not indicated for primary treatment of depressive states. It is not an antipsychotic agent, although it has been used as adjunctive therapy in some psychotic patients.

Dosage: One 350 mg. capsule, 3 times daily and two at bedtime is suggested as the adult starting dose. Adjust to suit individual requirements. Daily doses above 3000 mg. are not recommended.

Contraindications: Known hypersensitivity to tybamate. Since no studies have been done with this drug in human pregnancy, it should not be used in pregnancy unless the potential benefit outweighs the risk.

Warnings: Administer cautiously to patients receiving phenothiazines or other CNS depressants or having history of convulsive seizures (See Adverse Reactions). Consider possibility of additive actions with alcohol or other psychotropic agents, particularly phenothiazines or MAO inhibitors.

Precautions: Avoid abrupt withdrawal after prolonged use, although withdrawal symptoms have not been reported to date. Exercise caution in addiction-prone individuals. If symptoms of hypersensitivity occur, discontinue at once and initiate appropriate symptomatic treatment. Avoid activities requiring optimal mental alertness if drowsiness or vertigo are present. As with any new drug, use cautiously in patients with history of drug allergies, blood dyscrasias, and hepatic or renal disease; periodic measurements of hepatic, hematopoietic and renal function should accompany prolonged and/or high doses.

Adverse Reactions: Most frequent reactions, rarely requiring discontinuation of tybamate, include drowsiness, dizziness, nausea, insomnia, and euphoria. There have been a few reports of skin rash, urticaria, and pruritus. Rare side effects include hyperactivity, fidgetiness, flushing, and tachycardia, suggesting excessive stimulation; also ataxia, unsteadiness, confusion, feeling of unreality, "panic reaction," fatigue, headache, paresthesias, vertigo, gastrointestinal disturbances, glossitis, and dry mouth. Grand mal or petit mal seizures have been reported in a few hospitalized psychotic patients receiving tybamate (up to 6000 mg. daily) together with phenothiazines and other psychotropic agents, but not with tybamate alone. Consider the possibility of rare, serious adverse reactions such as may occur with the related drug, meprobamate. If excessive amounts are ingested, gastric lavage and symptomatic therapy, including central stimulants as necessary, are recommended. Before prescribing, consult package circular.

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References: 1. Jaffe, J. H.: in Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, 3rd ed., 1965, pp. 279-280. 2. Woods, L. A., in Drill, V. A.: Pharmacology in Medicine, 1958, pp. 226-227. 3. Goth, A.: Medical Pharmacology, 2nd ed., 1964, pp. 336-337. 4. Beckman, H.: Pharmacology, 2nd ed., 1961, pp. 180-183. 5. LaBrecque, D. C.: Curr. Ther. Res. 8: 106-109, 1966. 6. Dunlop, E.: J. Amer. Geriat. Soc. *16*:343-349, 1968.

The Differential Diagnosis of Sudden Cerebral Deficit*

One of the more perplexing problems in medicine is the sudden abrupt alteration in cerebral function of a patient. These changes are variable and may consist of simple loss of consciousness, sudden vertigo, motor paralysis, sensory irritation or deficit, aphasia, visual loss, diplopia, dysarthria, dysphagia or incoordination. These are the more common forms and each is quite frequently encountered. These deficits may clear or persist. Those that clear may represent a seizure discharge, but more often in the older age group they are manifestations of ischemia or infarction of the parenchyma of the brain.

Seizures

The factors which favor the diagnosis of a seizure are classical. Previous history of similar deficits can be expected in seizure disorders. The history of progression from the described deficit to unconsciousness of short duration some time in the past is evidence of a seizure. The unconscious period of such a seizure often includes clonic or tonic muscle movement, incontinence or a fall; or it is followed by a short period of confusion, headache or drowsiness. If the diagnosis is seizure there should be a suggestive history as to etiology.

Trauma

If mechanical trauma is to be incriminated, it should have produced a period of unconsciousness requiring medical observation and/or hospitalization with some post-traumatic symptoms of headache, nausea or vomiting and a period of retrograde amnesia.

Infection

If infection is to be considered significant, there must have been an episode requiring hospitalization for known meningitis or encephalitis or an established exanthematous disease with associated "fever convulsions", delirium or coma.

Neoplasm

If a new growth is to be accepted as the etiology, then progressive focal neurological deficit needs historical documentation. Then and only then is the diagnosis of a seizure to be entertained in a patient with this type of complaint.

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*Presented at the Minnesota Academy of General Practice Convention, Hotel Radisson, Minneapolis, Minnesota.

Cerebral Infarctions

If the sudden cerebral deficit does not fit the criteria of seizure but still persists as a deficit or has caused concern to the patient it must be considered a suspect cerebral infarction.

Cerebral infarctions generally occur deep within the white matter of the hemisphere, adjacent to the basal nuclei.

Motor System

Such infarctions may directly involve the corticospinal and corticobulbar pathways which control movement of the contralateral side of the body, but many do not. Those which do not involve the motor system cannot be expected to appear as a classical "stroke syndrome." The infarct which lies adjacent to the motor pathways or marginally in these pathways may produce only a transient motor deficit. Many of these will leave a most subtle persisting deficit, one which is found only on very careful neurological examination. If after a sudden hemiparesis which has "cleared" there is a minimal hyperreflexia, a suggestive Babinski sign or a loss of motor endurance, then it becomes sufficient evidence to substantiate a diagnosis of infarction.

Sensory Area

If the sudden cerebral deficit consists only of a sensory hallucination or deficit with minimal or no motor component, then the possibility of the infarct lying within the thalamoparietal radiations should be considered. A deficit of the sensory realm is quickly accommodated to by the patient, and only on a searching neurological examination will one find evidence of persisting damage. Lesions within this system may produce an astereognosis* of a contralateral side; the patient may not be able to identify objects placed in the hand by non-visual clues alone. Numbers written on the arms or hands, out of his view, may not be identified correctly on one side of the body. Fixed position of his extremities, the outstretched hands, may not be held symmetric when the eyes are shut. These findings may be as good as a paralysis for establishing a diagnosis of infarction of a more posterior site. Even more subtle sensory deficits of a very minimal hemihypesthesia or a hemihypalgesia may signify an infarct.

Visual Field

If the complaint is visual then tangent screen examination of the visual fields becomes mandatory. Patients, especially of the younger adult group, who develop a field defect may learn to accommodate rapidly and be unaware that a deficit persists. Tangent screen examination produces information which may well localize the lesion.

Aphasias

Sudden aphasias must be examined most carefully. Here the patient's own account is of great value: he may tell you he no longer can calculate or read or comprehend spoken words as rapidly as before. He may no longer be able to "find words" or to name objects or symbols as automatically as previously. This history is evidence of a cerebral infarction in the region of speech formulation, the posterior left hemisphere.

If the transient cerebral deficit has been one of diplopia, facial paresis, facial paresthesias or bulbar deficit and/or incoordination, then the diagnosis will be infarction; seizures do not often have such patterns. To detect a persisting deficit becomes most important since it determines the therapy. If it is overlooked it may well jeopardize the medical well-being of the patient.

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*See Test Your Word Score Page 1637.

Posterior Circulation Infarction

Basilar Vertebral Vessels

A transient or partial bullar palsy strongly suggests a vascular deficit in the distribution of the basilar vertebral circulation. This deficit associated with true vertigo is even more confirmatory. Previous history of alternating hemimotor, hemisensory or hemianoptic defect also incriminates this major circulation as the source of the pathology. True "dropping spells" also are almost exclusively due to basilar vertebral pathology in the older age group.

Superior Cerebellar Artery

Sudden transient or persisting diplopia associated with a unilateral incoordination should lead one to conclude that the vascular bed perfused by the Superior Cerebellar Artery has manifest ischemia or infarction. Other signs of this lesion are variable and unreliable.

Anterior Inferior Cerebellar Artery

Sudden facial paralysis and/or vertigo which remisses requires a careful search for unilateral cerebellar incoordination which would signify an infarct in the anterior inferior cerebellar artery distribution.

Posterior Inferior Cerebellar Artery

The sudden lateral medullary syndrome, the Wallenberg syndrome, consisting of a loss of bulbar function with vertigo and dysphagia, an ipsilateral facial hypesthesia, ipsilateral incoordination and contralateral body hypesthesia may rapidly subside, leaving only a minimal deficit. The presence of even a subtle incoordination confirms the fact that an infarct has occurred and permits the indicated therapy to be initiated without jeopardizing the health of the patient.

These, the clinically common forms of sudden cerebral deficit, are not difficult to diagnose. It is more difficult when no signs remain and the area involved is truly "silent." The concept of "transient ischemic attack" is probably the term to be applied to these infarcts which occur in areas of the brain which do not have direct externalization of their function in terms of motor, sensory, speech or visual performance.

George C. Flora, M.D.*
Minneapolis, Minnesota

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*Associate Professor of Neurology, University of Minnesota Medical School, Minneapolis, Minnesota.

Thought

Few people think more than two or three times a year. I have made an international reputation by thinking once or twice a week.—George Bernard Shaw

Pertofrane® desipramine hydrochloride

Indication. Mental depression.

Contraindications: Do not use MAO inhibitors concomitantly or within 2 weeks of the use of this drug. Hyperpyretic crises or severe convulsive seizures may occur with such combinations; potentiation of adverse reactions can be serious or even fatal.

When substituting Pertofrane in patients receiving an MAO inhibitor, allow an interval of at least 14 days. Initial dosage in such patients should be low and increases should be gradual and cautiously prescribed.

The drug is contraindicated following recent myocardial infarction and in patients with a known hypersensitivity to tricyclic antidepressants.

Warning: Activation of psychosis may occasionally be observed in schizophrenic patients. Due to atropine-like effects and sympathomimetic potentiation, use only with the greatest care in patients with narrow-angle glaucoma or urethral or ureteral spasm.

Do not use in patients with the following conditions unless the need outweighs the risk: severe coronary heart disease with EKG abnormalities, progressive heart failure, angina pectoris, paroxysmal tachycardia and active seizure disorder (may lower seizure threshold).

Desipramine and the parent compound, imipramine, have been shown to block the action of guanethidine and related adrenergic neuron-blocking agents.

Hypertensive episodes have been observed during surgery.

The concurrent use of other central nervous system drugs or alcohol may potentiate adverse effects. Since many such drugs may be used during surgery, desipramine should be discontinued prior to elective procedures.

Caution patients on the possibility of impaired ability to operate a motor vehicle or dangerous machinery.

Do not use in women who are or may become pregnant unless the clinical situation warrants the potential risk, and do not use in patients under 12 years of age.

Because of increased sensitivity to the drug, use lower than-normal dosage in adolescent and geriatric patients.

Precautions. Potentially suicidal patients require careful supervision and protective measures during therapy. Discontinuation of the drug may be necessary in the presence of increased agitation and anxiety shifting to hypomanic or manic excitement.

Atropine-like effects may be more pronounced (e.g. paralytic ileus) in susceptible patients and in those receiving anticholinergic drugs (including antiparkinsonism agents).

Prescribe cautiously in hyperthyroid patients and in those receiving thyroid medications; transient cardiac arrhythmias have occurred in rare instances.

Periodic blood and liver studies should supplement careful clinical observations in all patients undergoing extended courses of therapy.

Adverse Reactions. The following have been reported: *Nervous System:* dizziness, drowsiness, insomnia, headache, disturbed visual accommodation, tremor, unsteadiness, tinnitus, paresthesias, changes in EEG patterns, epileptiform seizures, mild extrapyramidal activity, falling and neuromuscular incoordination. A confusional state (with such symptoms as hallucinations and disorientation), particularly in older patients and at higher dosage, may require discontinuation of the drug. *Gastrointestinal Tract:* anorexia, dryness of the mouth, nausea, epigastric distress, constipation and diarrhea. *Skin:* skin rashes (including photosensitization), perspiration and flushing sensations. *Liver:* rare cases of transient jaundice (apparently of an obstructive nature) and liver damage. If jaundice or abnormalities in liver function tests occur, discontinue the drug and investigate. *Blood Elements:* bone-marrow depression, agranulocytosis, thrombocytopenia and purpura. If these occur, discontinue the drug. Transient eosinophilia has been observed. *Cardiovascular System:* orthostatic hypotension and tachycardia. Carefully supervise patients requiring concomitant vasodilating therapy, particularly during initial phases. *Genitourinary System:* urinary frequency or retention and impotence. *Endocrine System:* occasional hormonal effects, including gynecomastia, galactorrhea and breast enlargement, and decreased libido and estrogenic effect. *Sensitivity:* urticaria and rare instances of drug fever and cross-sensitivity with imipramine.

Dosage. All patients except geriatric and adolescent: 50 mg. t.i.d. (150 mg. daily). Dosage may be increased up to 200 mg. daily. Geriatric and adolescent patients should usually be started with lower dosage (25 to 50 mg. daily) and may not tolerate higher doses. Dosage may be increased up to 100 mg. daily.

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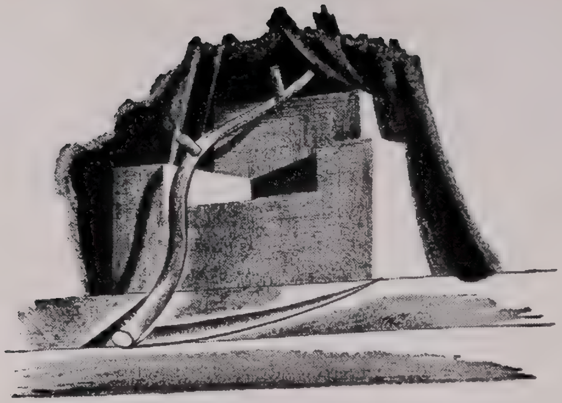

In Memoriam

The eternal stars shine out as soon as it is dark enough.—Carlyle

C. KENNETH COOK, M.D.

Dr. C. Kenneth Cook, 68, St. Paul surgeon, died July 2. A native of New London, Iowa, Dr. Cook was a resident of St. Paul for 37 years. He retired after 30 years from his Payne Avenue medical practice in 1962. He was an alumnus of the University of Iowa and graduated from the University of Michigan Medical School in 1927.

Dr. Cook was a member of the Ramsey County Medical Society, the American Medical Association, a fellow of the American College of surgeons and the International College of Surgeons, and an Associate Member of the Minnesota State Medical Association. He was chief of staff at St. Johns' Hospital in 1951 and 1952.

He is survived by his wife, a daughter and a son.

ARTHUR WILLIAM NUETZMAN, M.D.

Dr. Arthur W. Nuetzman, 66, a practicing physician and surgeon in Faribault for 35 years, died May 24. A graduate of the University of Minnesota School of Medicine, Dr. Nuetzman interned at the Charles T. Miller Hospital in St. Paul before establishing his Faribault practice.

Dr. Nuetzman had served as Rice County coroner for over 20 years and had been physician for the Minnesota State Braile and Sight Saving School in Faribault since 1935. He was a member of the medical staff of the Rice County District One Hospital, the Rice County Medical Society, the Minnesota State Medical Association and the American Medical Association.

He is survived by his wife and one son.

HAMLIN A. N. MATTSON, M.D.

Dr. Hamlin A. N. Mattson, 69, Minneapolis surgeon for 37 years, died June 28. Born in Tacoma, Washington, Dr. Mattson obtained his medical degree at the University of Minnesota.

He was a past president of the American Swedish Institute, a member of the Hennepin County Medical Society, the Minnesota State Medical Association and the American Medical Association.

He is survived by his wife, a son and two daughters.

CLAYTON K. WILLIAMS, M.D.

Dr. Clayton K. Williams, 78, St. Paul physician, died June 27, following a short illness. Born in Minneapolis but a resident of St. Paul for the past 40 years, Dr. Williams received his medical degree from the University of Minnesota.

He was a former secretary and a past president of the Ramsey County Medical Society and was a member of the Minnesota Academy of Medicine, American Medical Association and a 50 Club and Life Member of the Minnesota State Medical Association.

He is survived by his wife.

DAN W. FISHER, M.D.

Dr. Dan W. Fisher, 65, St. Paul physician, died May 14. Born in Ellwood City, Pennsylvania, Dr. Fisher obtained his medical degree at the University of Michigan.

He was a member of the Ramsey County Medical Society, the American College of Physicians, the Minnesota State Medical Association and the American Medical Association.

Dr. Fisher is survived by his wife, a son and a daughter.

RAMBY C. RASMUSSEN, M.D.

Dr. Ramby C. Rasmussen, 78, St. Paul surgeon, died May 23. Born in Denmark, Dr. Rasmussen received his medical degree from the University of Minnesota.

He was a member of the Ramsey County Medical Society, the American Medical Association and the Minnesota State Medical Association.

Dr. Rasmussen is survived by his wife and a son.

JOSEPH L. MARTINEAU, M.D.

Dr. Joseph L. Martineau, 81, St. Paul surgeon, died June 6. Born in St. John, North Dakota, Dr. Martineau had lived in St. Paul for the past 55 years. He established a medical practice in St. Paul in 1915.

He was a member of the American Medical Association, the Ramsey County Medical Society, the American Academy of General Practice, and a 50 Club and Life Member of the Minnesota State Medical Association. His medical degree was received from Rush Medical College, University of Chicago.

He is survived by his wife, three daughters and a son.

WILLIAM B. McMURTRIE, M.D.

Dr. William B. McMurtrie, 71, Minneapolis physician, died May 26. A graduate of the University of Minnesota Medical School, Dr. McMurtrie practiced in Marble and Hutchinson, Minnesota, before opening offices in Minneapolis.

He was a member of the Hennepin County Medical Society, the Minnesota State Medical Association and the American Medical Association.

He is survived by his wife and two daughters.

CLARENCE O. MALAND, M.D.

Dr. Clarence O. Maland, 87, Minneapolis obstetrician and gynecologist at the Swedish Hospital, died June 14.

He was assistant professor of obstetrics and gynecology at the University of Minnesota Medical School, during his tenure at the Swedish Hospital.

Dr. Maland was a member of the College of Surgeons, the Hennepin County Medical Society and American Medical Association and a 50 Club and Life Member of the Minnesota State Medical Association.

He is survived by his wife and a daughter.

SOLVEIG T. GISLASON, M.D.

Dr. Solveig T. Gislason, 78, St. Peter physician and teacher, died June 12. A graduate of the University of Minnesota Medical School, she first practiced medicine in Marshall, when her husband, Judge Gislason, was assigned there, and later practiced in New Ulm. From there she went to St. Peter where after practicing for 15 years retired from practice last year.

She was a member of the Nicollet-LeSueur County Medical Society, the Minnesota State Medical Association and the American Medical Association.

Dr. Gislason was survived by three sons and a daughter.

LESLIE CAPLAN, M.D.

Dr. Leslie Caplan, 61, Minneapolis psychiatrist, died August 4. He was a graduate of Ohio State University and the Ohio State University Medical School.

A clinical associate professor at the University of Minnesota and a consultant at the Veterans Hospital in Minneapolis, Dr. Caplan was a member of the American Medical Association, the Minnesota State Medical Association, the Hennepin County Medical Society, a fellow of the American Psychiatric Association and a past secretary of the State Association.

He is survived by his wife and two daughters.

DAVID S. THORSEN, M.D.

Dr. David S. Thorsen, director of the Wilder Child Guidance Clinic, died July 4. He was 52.

Born in Minneapolis, Dr. Thorsen attended the University of Minnesota and received his medical degree from the University's College of Medicine. In recent years he had been a consultant to the Hennepin County Welfare Department, the Lutheran Social Service and the Washington County Juvenile Court.

Dr. Thorsen was a member of the American Medical Association, the Minnesota State Medical Association and the Hennepin County Medical Society.

He is survived by his wife, three daughters and two sons.

RICHARD H. SEARL, M.D.

Dr. Richard H. Searl, 36, Faribault physician, died June 19. He graduated from the University of Kansas Medical School in 1957 and interned at Ancker Hospital in St. Paul.

Dr. Searl was presently serving as secretary-treasurer of the Southern Minnesota Medical Association and was president of the Southern Minnesota Chapter of the Minnesota Academy of General Practice, chairman of the Membership and Credentials Committee of the Minnesota Academy of General Practice and chairman of the General Practice Club at the University of Minnesota. He was also a member of the American Medical Association, the Minnesota State Medical Association and the Rice County Medical Society.

He is survived by his wife, a son and daughter.

WILLIAM W. WILL, M.D.

Dr. William W. Will, 90, Bertha physician for more than 50 years, died July 11. Born in Blue Earth County, he received his medical degree from the University of Minnesota Medical School.

For fifteen years he was president of the Todd County Medical Club. In addition, Dr. Will was a member and former president of the Upper Mississippi Medical Society; member and former president of the Northern Minnesota Medical Society; member, president for one year, councilor, 12 years, speaker of the House of Delegates for nine years and a Life and 50 Club Member of the Minnesota State Medical Association; trustee and vice president of the Minnesota Medical Foundation of the University of Minnesota; member and director, Minnesota State Sanitary Conference; member of the Fair Oaks Lodge Sanatorium Commission and a Fellow of the American College of Surgeons and the International College of Surgeons.

Dr. Will is survived by two sons and daughters.

CHARLES L. SHERMAN, M.D.

Dr. Charles L. Sherman, 92, retired Luverne physician and surgeon, died July 8. Born at Canton, South Dakota, Dr. Sherman received his medical degree from Barnes Medical School in St. Louis.

Dr. Sherman was one of the men who foresaw the need of a sanitarium for tuberculosis in southwestern Minnesota and had been active in the organization of an eight-county district to fight the dreaded disease.

The late Governor Christianson appointed him to serve on the Minnesota Board of Medical Examiners in 1927, a position which he held until a few years ago. He served as president of the Southwestern Minnesota Medical Association, was president of the Southern Minnesota Medical Association, and headed at one time the Sioux Valley Medical Society. He was a member of the American Medical Association and was a 50 Club and Life Member of the Minnesota State Medical Association.

Dr. Sherman is survived by his wife and son.

FREDERICK N. SOLSEM, M.D.

Dr. Frederick N. Solsem, 90-year-old Spicer physician, died July 7. He attended Loyola University Medical School in Chicago and resumed his private practice at Spicer in the early 1930s.

He was a member of the American Medical Association and Kandiyohi-Swift-Meeker Medical Society and a 50 Club and Life Member of the Minnesota State Medical

Association.

Dr. Solsem is survived by his wife and one daughter.

THOMAS S. McCLANAHAN, M.D.

Dr. Thomas S. McClanahan, 77, a long-time White Bear Lake physician, died August 1, after a short illness. He was born in Kirkwood, Illinois, and had been a resident of St. Paul since 1919, when he began his medical practice.

He was a member of the American Medical Association and Ramsey County Medical Society and a 50 Club and Life Member of the Minnesota State Medical Association. A long-time staff member at St. John's Hospital, Dr. McClanahan was chief of staff there from 1954 to 1955. He retired in 1966.

Dr. McClanahan is survived by his wife, two daughters and a son.

ROBERT P. CARON, M.D.

Dr. Robert P. Caron, 70, Minneapolis surgeon, died August 3. Born in Illinois, Dr. Caron attended the University of Illinois Medical School, graduating in 1925.

He was a member of the American Medical Association and the Hennepin County Medical Society and a Life Member of the Minnesota State Medical Association.

Dr. Caron is survived by his wife and daughter.

DAVID I. SEIBEL, M.D.

Dr. David I. Seibel, 47, assistant professor of obstetrics and gynecology at the University of Minnesota, died August 17. A graduate of the City College of New York and the University of Rochester, New York Medical School, Dr. Seibel came to Minneapolis twenty-two years ago.

He was a diplomate of the American Board of Obstetrics and Gynecology and a member of the American Medical Association, the Minnesota State Medical Association, the Minnesota State Obstetrics and Gynecology Association, Hennepin County Medical Society, American Society of Cystology and the Minnesota Medical Foundation.

Dr. Seibel is survived by his wife, two sons and a daughter.

EJVIND P. K. FENGER, M.D.

Dr. Ejvind Fenger, 72, of Chanhassen, director of tuberculosis services for the Minnesota State Department of Health since 1961, died July 25.

A nationally recognized clinical specialist in pulmonary diseases, he coordinated the state and local tuberculosis control services of the department and directed the tuberculosis control and treatment program in all state institutions for the Department of Public Welfare.

Born in Denmark, Dr. Fenger grew up in Askov, Minnesota. He received his medical degree from the University of Minnesota in 1924 and was on the medical staff of the Glen Lake Sanatorium for 36 years.

Dr. Fenger was one of only 91 board-certified, full-time specialists in pulmonary diseases in the nation. He was a member of the American Medical Association and the Hennepin County Medical Society and a Life Member of the Minnesota State Medical Association.

He is survived by his wife and two daughters.

HENRY WILLIAM MEYERDING, M.D.

Dr. Henry William Meyerding, 84, a member of the section of Orthopedic Surgery of the Mayo Clinic from 1910 to 1949, and professor of orthopedic surgery in the Mayo Graduate School of Medicine of the University of Minnesota, died August 27. Born in St. Paul, he received his doctor of medicine from the University of Minnesota. He went to Rochester in 1910 as special assistant to Doctors William J. Mayo, Charles H. Mayo and E. Starr Judd.

Dr. Meyerding received the degree of master of science in orthopedic surgery in 1918, the first to be given by the newly established Mayo Graduate School of Medicine of the University of Minnesota. From 1918 he was instructor in orthopedic surgery in the Mayo Graduate School of Medicine; from 1920 to 1922 he was assistant professor; from 1922 to 1937 he was associate professor; and from 1937 to 1949 he was professor. On his retirement in 1949 he became an emeritus professor.

In 1923 he prepared an exhibit on tumors of bone which became a permanent exhibit in the Wellcome Museum of Medical Sciences in London, England.

Among the many positions he held are: president of the Clinical Orthopaedic Society in 1926; president of the Southern Minnesota Medical Association, first national member chairman of the American Academy of Orthopaedic Surgeons. He was one of the founders of the World Medical Association in 1948 and was elected president of the International College of Surgeons in 1958; he was president of the American Fracture Association and had been chairman of the section on Orthopaedic Surgery of the American Medical Association.

He was a member of the Zumbro Valley Medical Society and an Associate and 50 Club Member of the Minnesota State Medical Association.

Dr. Meyerding is survived by four grand children and two great-grand children.

FRANCIS RAYMOND KEATING, M.D.

Dr. F. Raymond Keating, Jr., 58, and his wife were killed in an automobile accident September 13. He was a Mayo Clinic specialist in metabolic diseases and considered one of the top researchers in that field. A native of Philadelphia, Dr. Keating was graduated from Cornell University; became a resident at the Mayo Graduate School and in 1941 was appointed an assistant to the clinic staff.

He was a senior consultant at the Clinic and a professor in the University of Minnesota Mayo Graduate School of Medicine.

Dr. Keating was a member of the Zumbro Valley Medical Society, the American Medical Association and the State Medical Association.

". . . Now it is time to go—I to die and you to live; which of us is the happier is not known to anyone but God."—Socrates.

Some men succeed because they are destined to, but most men because they are determined to.—Jacob Braude: Speaker's Encyclopedia

INCORPORATED

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Book Reviews

That is a good book which is opened with expectation and closed with profit.—
Amos Bronson Alcott

PIE IN THE SKY; THE MAKING OF AN AIRLINE STEWARDESS. By Marcia Norgaard. 165 pp. 1969 Exposition Press. New York. $4.50

Marcia Norgaard, ex-airline stewardess for Northwest Airlines, has invented North American Airlines, suspiciously like Northwest Airlines, to provide the vehicle for what must be (to some extent) autobiography molded to the shape of a novel. Her story of Kip Miller's progress through stewardess training and into a flying career is so absorbing that I found the book impossible to put down. Minnesota readers will recognize the locale of much of the action in and around Wold Chamberlain Airport. I suspect Mrs. Norgaard's main purpose in writing this book was to publish her address to high school senior girls on a flying career for women. But with it she has professionally written an account of an interesting career. And I must remember to ask Mrs. Norgaard what she meant by her subtitle.

Reuben Berman, M.D.
Minneapolis, Minnesota

CHRONIC ULCERATIVE COLITIS. By J. Arnold Bargen, M.C., Pages: 123, Illustrations: 26, Publisher: Charles C Thomas, Springfield, Illinois.

This short monograph, Ulcerative Colitis, is an interesting review of a lifelong study by the author.

It is well organized and covers briefly the broad field of ulcerative colitis in six chapters. The index is not comprehensive but is adequate for the size of the monograph. For a fascinating few hours of study or review it is well worth possessing.

Carl O. Rice, M.D,
Minneapolis, Minnesota

YOUR COMMUNITY HOSPITAL. By Robert Walsh. Beacon Press, $5.95.

This book, written by Robert E. Walsh, a reporter, is a successful attempt to rid the general public of the outmoded idea that a hospital is a collection of beds and medical equipment to be used only in spells and may help the public to better understand the emerging role of the hospital as a coordinating point for the health care of the community.

The book is recommended for reading by lay individuals who either contemplate hospital care or who are interested in the hospital as a place in the community.

Most people give little serious thought to the state of their community hospital until a health emergency arises; then when an understanding of how hospitals work would be most useful, their confusion and lack of information prevent them from utilizing its benefits efficiently. YOUR COMMUNITY HOSPITAL was written in order to improve this situation and to help American communities develop an active interest and participation in the affairs of their hospitals.

Mr. Walsh has accurately portrayed the community hospital. This is evident by the insight that he has gained about the problems and successes, the shortcomings and controls that affect the organization of a modern hospital. Questions are many but not uncomplimentary.

The author gives an excellent definition of the physician for the benefit of the layman. He illustrates some of the dilemmas physicians face, such as house calls, fees, etc. He provides an excellent explanation of the hospital-based specialist.

His conclusions are optimistic and, although he portrays some situations that are less satisfactory than they might be, his picture of a hospital is not as frightening as the occasional scandal report insists.

Frank S. Walter*
Minneapolis, Minnesota

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*Administrator, St. Barnabas Hospital.

TOBACCO AND YOUR HEALTH. Author: Harold S. Diehl, M.D., Special Consultant, American Cancer Society. Publisher: McGraw-Hill Book Company, New York.

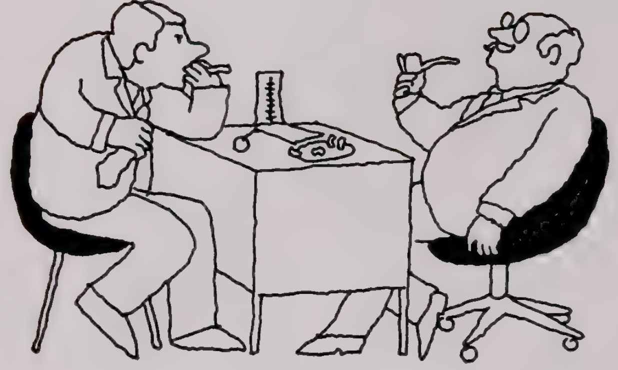
This interestingly compiled monograph pertaining to the ill effects of cigarette smoking makes interesting, informative and worthwhile reading.

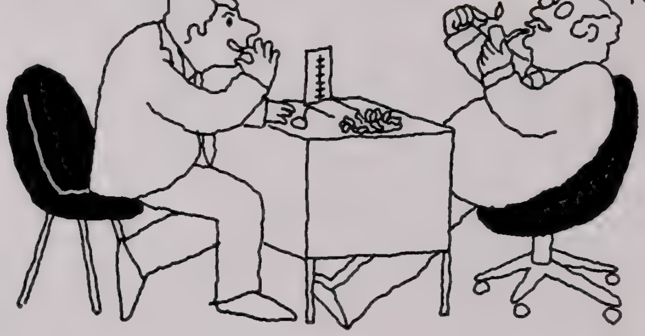
The habit of smoking is extremely difficult to eliminate but, after one has read this monograph and learned the numerous hazards, one should also realize the tremendous value of eliminating the habit. It is interesting to note that after one has managed to control the smoking habit the danger from carcinoma of the lung disappears in large part. Unfortunately, some of the less spectacular diseases, namely chronic bronchitis and peripheral vascular changes which can be almost as bad as cancer because of the continuing prolonged harmful effects, are not as easily eliminated after the cessation of smoking.

Surely this monograph can be advantageously recommended to the smoker who desires to discontinue the habit.

Carl O. Rice, M.D.
Minneapolis, Minnesota

The Apprehensive Hypertensive


WELL, YOU HAVE WHAT WE CALL MODERATE HYPERTENSION– HIGH BLOOD PRESSURE. NOW I DON'T WANT YOU TO WORRY, BUT WE ARE GOING TO HAVE TO CHANGE A FEW LIVING HABITS. FIRST, WE'RE GOING TO HAVE TO CUT OUT SMOKING–ALTOGETHER.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Regroton®: chlorthalidone 50 mg., reserpine U.S.P. 0.25 mg. *Indications:* Hypertension. *Contraindications:* History of mental depression, hypersensitivity, and most cases of severe renal or hepatic diseases. *Warning:* With the administration of enteric-coated potassium supplements, which should be used only when adequate dietary supplementation is not practical, the possibility of small-bowel lesions (obstruction, hemorrhage, and perforation) should be kept in mind. Surgery for these lesions has frequently been required and deaths have occurred. Discontinue coated potassium-containing formulations immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occur. Discontinue one week before electroshock therapy, and if depression or peptic ulcer occurs. *Use in pregnancy:* Because chlorthalidone may cross the placental barrier and appear in cord blood and thiazides may appear in breast milk, this drug should be used with care in pregnant patients and nursing mothers. When used in women of childbearing age, the potential benefits of the drug should be weighed against the possible hazards to the fetus. Use of chlorthalidone may result in fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. Inc respiratory secretions, nasal congestion, cyanosis and anorexi occur in infants born to reserpine-treated mothers. *Precautions:* pertensive therapy with this drug should always be initiated cau in postsympathectomy patients and in patients receiving gan blocking agents, other potent antihypertensive drugs, or curare. F dosage of concomitant antihypertensive agents by at least one-h avoid hypotension during surgery, discontinue therapy with this two weeks prior to elective surgical procedures. In emergency s use, if needed, anticholinergic or adrenergic drugs or other sup measures as indicated. Because of the possibility of progres renal damage, periodic kidney function tests are indicated. Disc if the BUN rises or liver dysfunction is aggravated. Hepatic com be precipitated. Electrolyte imbalance, sodium and/or potassi pletion may occur. If potassium depletion should occur during th the drug should be discontinued and potassium supplements provided the patient does not have marked oliguria. Take particul in cirrhosis or severe ischemic heart disease and in patients re

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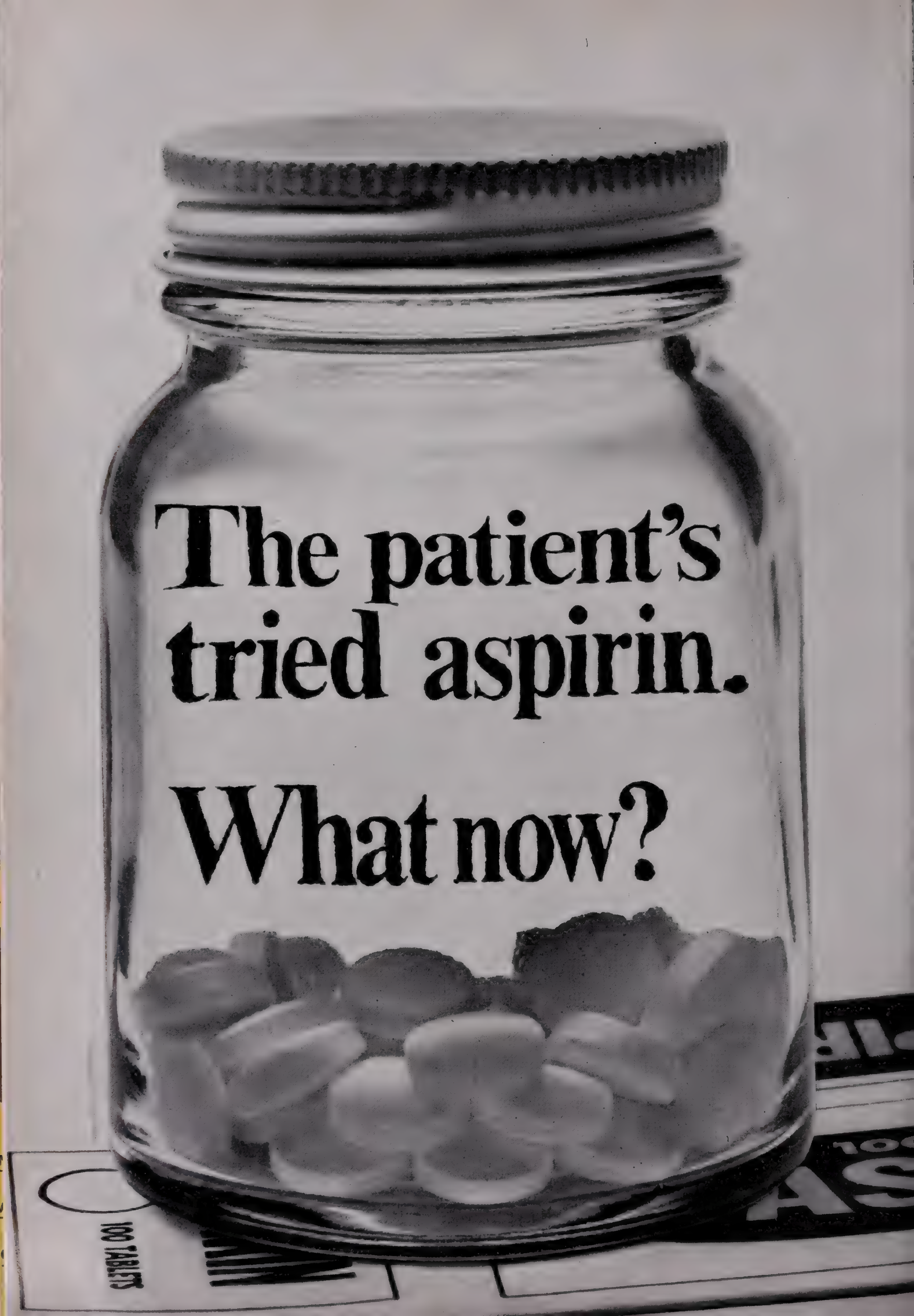
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IN BRIEF

Contraindications: History of sensitivity or severe intolerance to aspirin, meprobamate or ethoheptazine citrate.

Warnings: USE IN PREGNANCY: Safety for use during pregnancy or lactation has not been established; therefore, it should be used in pregnant patients or women of child-bearing age only when the physician judges its use essential to the patient's welfare.

Precautions: Keep out of reach of children. Not recommended for patients 12 years old or less. Carefully supervise dose and amounts prescribed, especially for patients prone to overdose themselves. Excessive prolonged use of meprobamate in susceptible persons—as alcoholics, ex-addicts, severe psychoneurotics—has resulted in dependence or habituation. Withdraw gradually after prolonged excessive dosage to avoid possibly severe withdrawal reactions including epileptiform seizures. Warn patients of possible reduced alcohol tolerance, with resultant slowed reactions and impaired judgment and coordination. If drowsiness, ataxia or visual disturbances (impairment of accommodation and visual acuity) occur, reduce dose. If symptoms persist, patients should not operate machinery or drive. After meprobamate overdose, prompt sleep, reduction of blood pressure, pulse and respiratory rates to basal levels, and hyperventilation are reported. Give cautiously and in small amounts to patients with suicidal tendencies. Treat attempted suicide (has resulted in coma, shock, vasomotor and respiratory collapse and anuria) with gastric lavage and appropriate symptomatic therapy (CNS stimulants and pressor amines as indicated). Two instances of accidental or intentional significant overdosage with ethoheptazine and aspirin have been reported. These were accompanied by CNS depression (drowsiness and lightheadedness) but resulted in uneventful recovery. On basis of pharmacologic data, CNS stimulation could be anticipated, with nausea, vomiting and salicylate intoxication (requires induced vomiting or gastric lavage, specific parenteral electrolyte therapy for ketoacidosis and dehydration, and observation for hypoprothrombinemic hemorrhage [usually requires whole blood transfusions]).

Adverse Reactions: Ethoheptazine and aspirin may cause nausea with or without vomiting and epigastric distress in a small percentage of patients. Dizziness is rare at recommended dosage. Meprobamate may cause drowsiness, ataxia and rarely allergic or idiosyncratic reactions. These reactions, sometimes severe, can develop in patients receiving only 1 to 4 doses. Such patients may have had no previous contact with meprobamate and may or may not have an allergic history. Mild reactions are characterized by urticarial or erythematous maculopapular rash. Acute nonthrombocytopenic purpura with cutaneous petechiae, ecchymoses, peripheral edema and fever have been reported. If allergic reaction occurs, discontinue meprobamate; do not reinstitute. Severe reactions, observed very rarely, include fever, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (1 fatal case), anaphylaxis, stomatitis and proctitis (1 case) and hyperthermia. These cases should be treated symptomatically including, when indicated, such medication as epinephrine, antihistamine and possibly hydrocortisone. A few cases of leukopenia, usually transient, have been reported on continuous use. Rarely, aplastic anemia (1 fatal case), thrombocytopenic purpura, agranulocytosis, and hemolytic anemia have been reported, almost always in presence of known toxic agents.

Overdosage: See precautions section for management of overdosage.

Composition: 150 mg. meprobamate, 75 mg. ethoheptazine citrate and 250 mg. aspirin per tablet.

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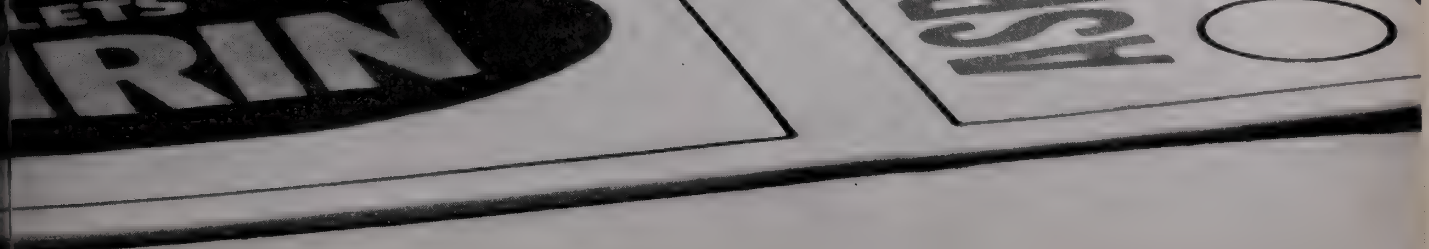

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Minnesota Medicine at a Glance

Treatment of Coronary Disease—*Edwards* Page 1587

Numerous advances in care of patients suffering from coronary artery disease have opened new avenues of treatment for several aspects of this widespread disease process. The anatomic limitations of these newer forms of treatment are discussed. Numerous fine photographs and photomicrographs clearly illustrate the problems discussed.

Thrombocytosis—*Silvis et al.* Page 1603

The records of 322 patients with thrombocytosis have been reviewed. The number of patients with thrombocytosis was 2.57 per cent of the hospital admissions for this period. Malignant disease was found in 64 per cent of the patients, whereas 36 per cent had benign conditions. Of the patients studied 9.9 per cent had thromboembolic complications after the thrombocytosis was discovered. Patients with thromboembolic disease had higher average platelet counts and hemoglobin concentration than those who did not develop this complication. The present study confirms the almost century-old observation that thrombocytosis is seen in a high number of patients with malignant disease. Although the mechanism of the platelet count elevation with malignant conditions is not clear, recognition of this association may be helpful in the diagnostic workup of patients.

Hematologic Toxicity of Chloramphenicol—*Mork* Page 1619

The magnitude of the chloramphenical mis-prescription problem is reviewed. A surprising number of delayed cases of myelogenous leukemia have occurred after non-fatal aplastic anemia following chloramphenical therapy.

Tumors in Children—*Mahour and Lynn* Page 1679

The authors present a brief but thorough survey of tumors in children, with statistical data pertinent to the differential diagnosis of these tumors as well as the clinical descriptions of each entity. They also include a review of the experience at the Mayo Clinic with soft tissue sarcomas of children from 1950 to 1965.

THEORY versus FACT

"However good a theory may be, it is never as good as the truth or as actual fact. I do not believe there is a single theory in physiology, or even in physics and chemistry, that is actually and absolutely true. Everything is merely relative. . . . It is therefore an excellent thing to have destroyed a theory. It is a step forward, and we must not quake when a fact destroys a theory, even our own—we must investigate. There is a discovery underneath, a revolution, as they say; for science is revolutionary, and does not advance by successive additions, as people believe it does."*

---

*Claude Bernard, as quoted by Jerome Tarshis in Claude Bernard, Father of Experimental Medicine, 1968.

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Donald A. Scholz, M.D.

NOVEMBER, 1969

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You made me
what I am today–
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Contraindications: Concurrently with MAO inhibitors, in patients hypersensitive to this drug; in emotionally unstable patients susceptible to drug abuse.

Warning: Although generally safer than the amphetamines, use with great caution in patients with severe hypertension or severe cardiovascular disease. Do not use during first trimester of pregnancy unless potential benefits outweigh potential risks.

Adverse Reactions: Rarely severe enough to require discontinuation of therapy, unpleasant symptoms with diethylpropion hydrochloride have been reported to occur in relatively low incidence.

As is characteristic of sympathomimetic agents, it may occasionally cause *CNS effects* such as insomnia, nervousness, dizziness, anxiety, and jitteriness. In contrast, CNS depression has been reported. In a few epileptics an increase in convulsive episodes has been reported.

Sympathomimetic *cardiovascular effects* reported include ones such as tachycardia, precordial pain, arrhythmia, palpitation, and increased blood pressure. One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride; this was an isolated experience, which has not been reported by others.

Allergic phenomena reported include such conditions as rash, urticaria, ecchymosis, and erythema.

Gastrointestinal effects such as diarrhea, constipation, nausea, vomiting, and abdominal discomfort have been reported.

Specific reports on the hematopoietic system include two each of bone marrow depression, agranulocytosis, and leukopenia.

A variety of miscellaneous adverse reactions have been reported by physicians. These include complaints such as dry mouth, headache, dyspnea, menstrual upset, hair loss, muscle pain, decreased libido, dysuria, and polyuria.

Convenience of two dosage forms: TEPANIL Ten-tab tablets: One 75 mg. tablet daily, swallowed whole, in midmorning (10 a.m.); TEPANIL: One 25 mg. tablet three times daily, one hour before meals. If desired, an additional tablet may be given in midevening to overcome night hunger. Use in children under 12 years of age is not recommended.

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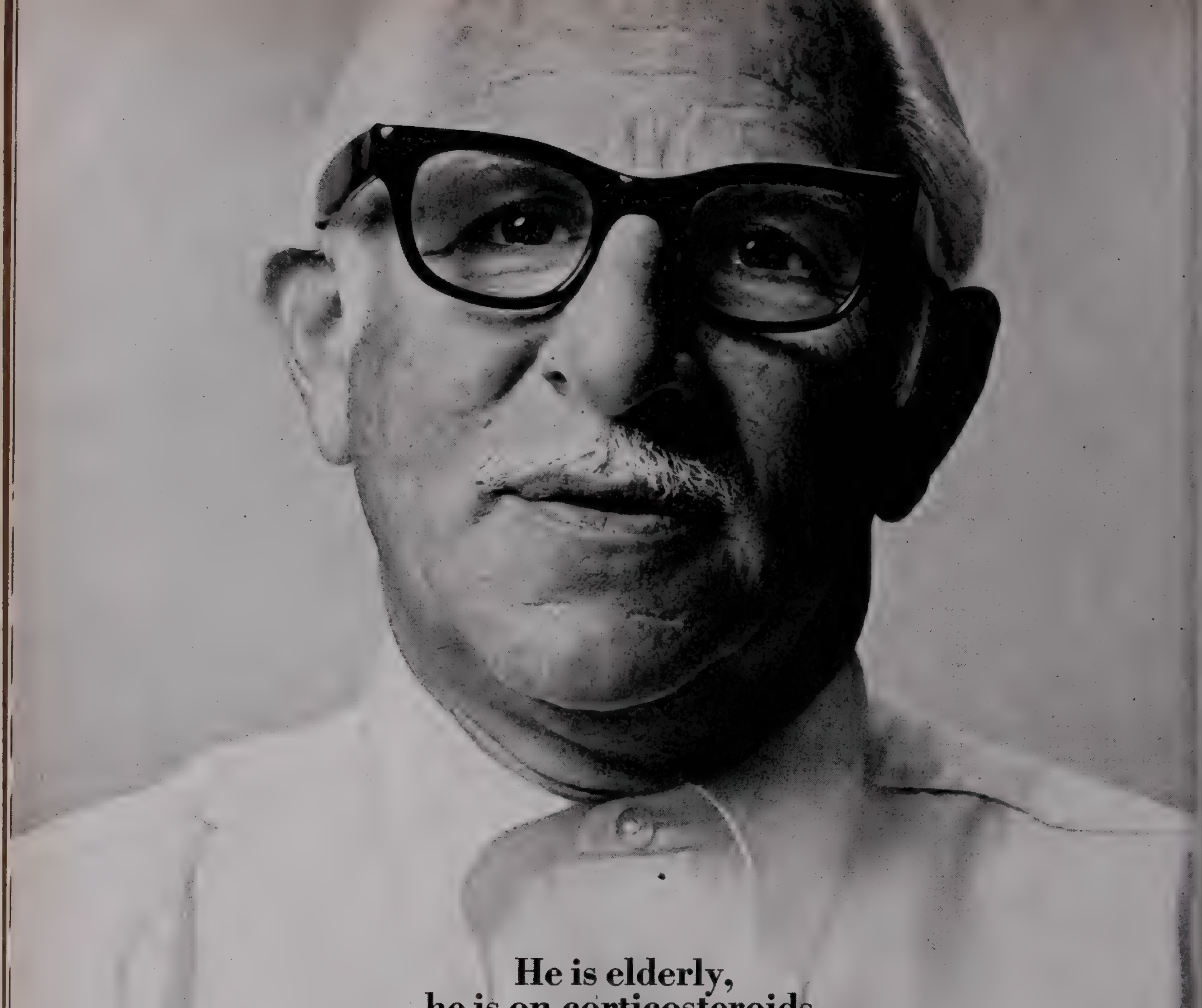

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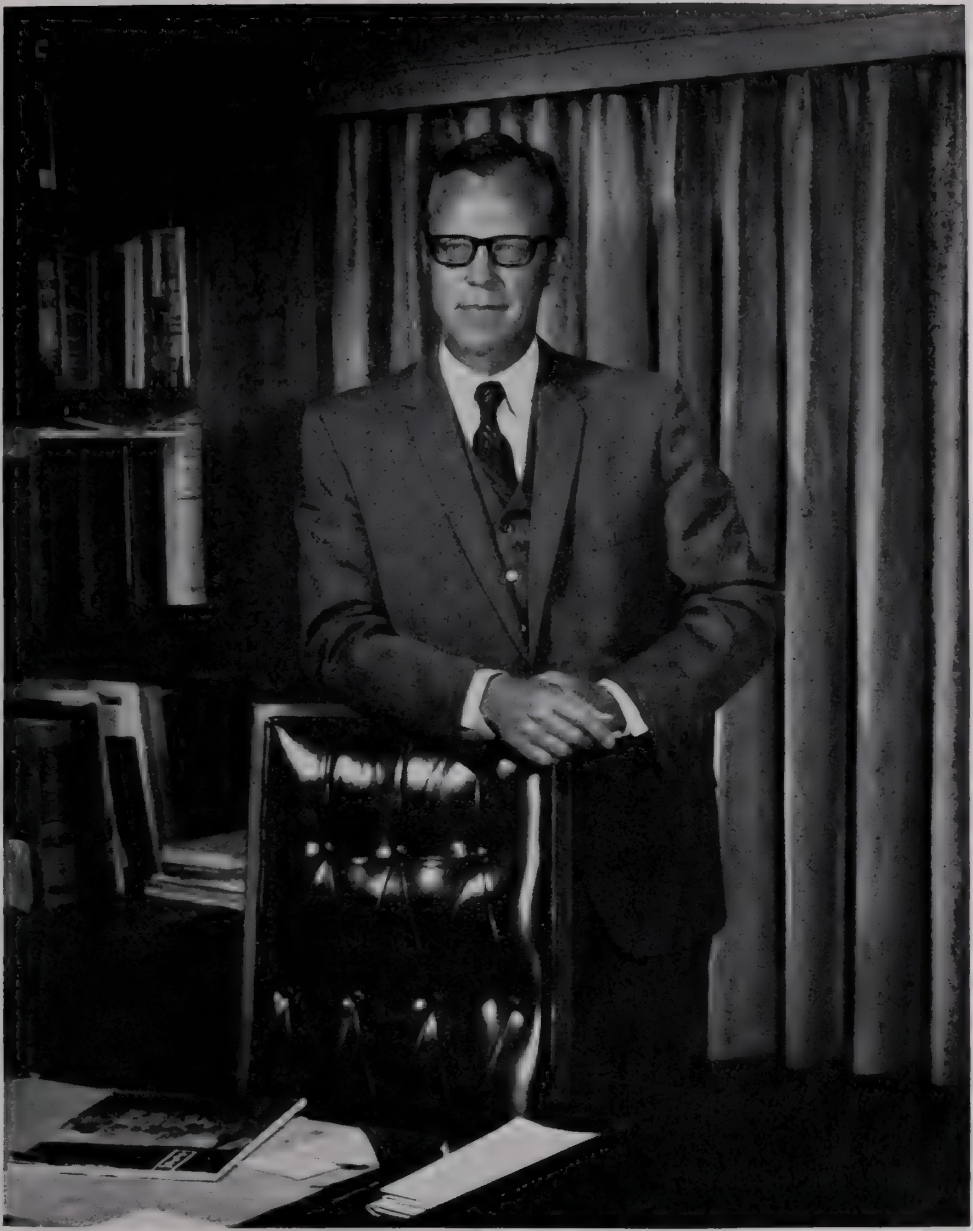
Meet the President



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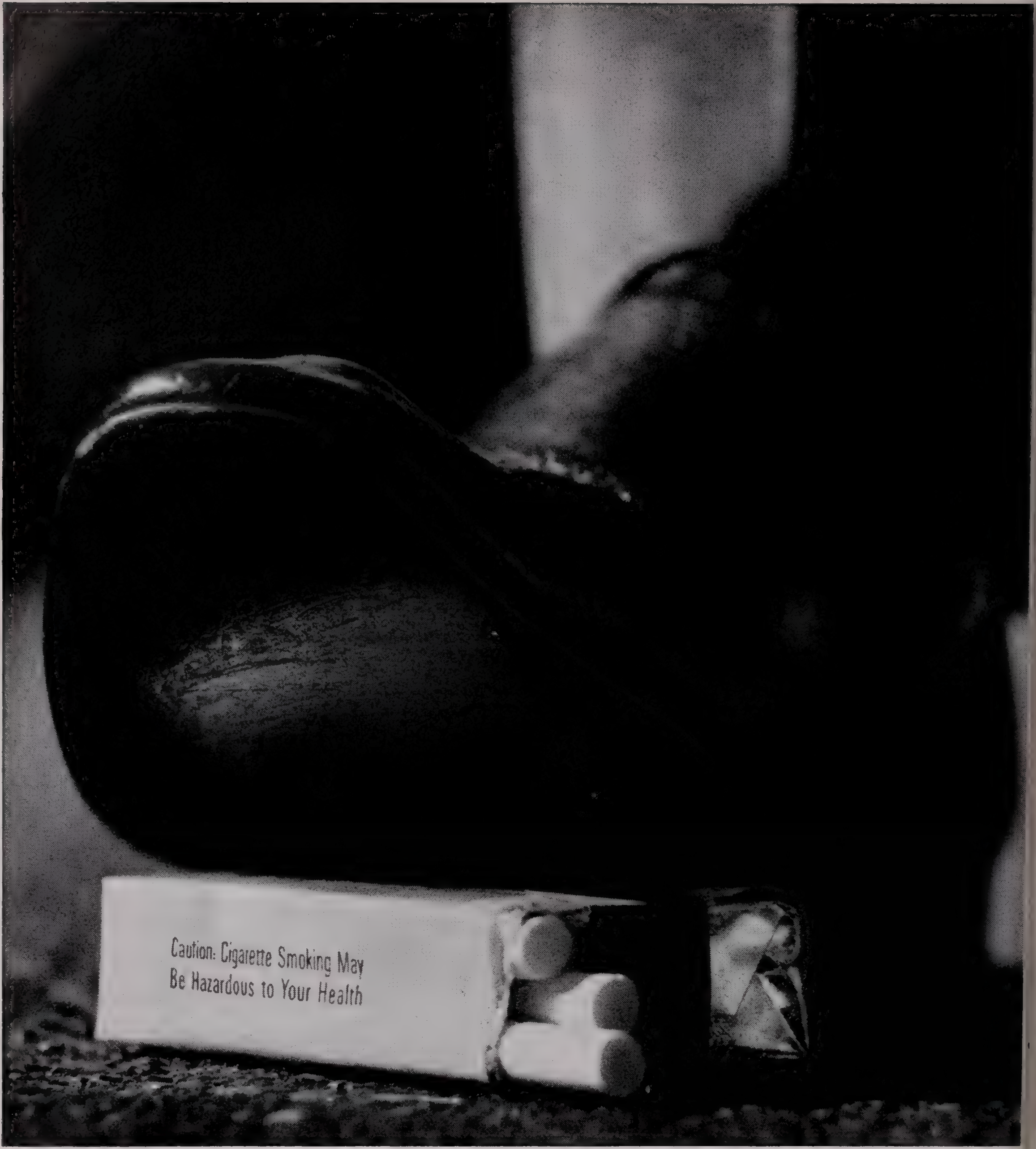
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President's Letter

Association of Minnesota Internists

THE ASSOCIATION OF MINNESOTA INTERNISTS is the State chapter of the American Society of Internal Medicine (ASIM). The National Society was formed in 1956 to provide internists with an organization to study and respond to socioeconomic and political forces affecting the cost, quality and availability of their services and to insure continuing professional competence of the internist in the practice of his speciality.

The action forming the new Society was supported by the American College of Physicians. The two Societies are now working closely through liaison committees from the presidential level on down. From a small beginning the Society has rapidly expanded and today numbers over 10,000 active members.

As all physicians soon discover, quality professional service cannot be separated from either the costs or the conditions under which it is provided.

The impact of Federal health care financing and the ever increasing governmental controls which are becoming more and more apparent should make us all realize that the things which are exerting major influences on our lives and on our goals in medicine are not happening in our offices but outside of them — largely in Washington, D. C.

We have recently heard the opening guns in a campaign to fix the blame for increasing Medicare costs. Even though Congress was warned that such would occur there is much feigned surprise today, and no small attempt is being made to place the blame for increasing costs on the physician. One of our aims is to vigorously evaluate the problems briefly referred to above and to find solutions not in recrimination but through constructive cooperation.

Health care has became a "right" of the American citizen. The mushrooming demands for medical services are beginning to tax not only the ingenuity but the physical endurance of the most dedicated physician. Either we must devise new methods of practice to handle all those demanding services or the government will do it for us.

In this sector the American Society of Internal Medicine is moving ahead in planning for the training of para-medical personnel. Much time and thought are going into methods of developing and using multiphasic health screening procedures. Labor management committees are helping to write new contracts that will bring medical care into proper perspective. Ways of increasing the number of medical graduates are being actively studied.

Propaganda fostered by both the Federal government and the prepaid hospital plans has made the use of the hospital bed much like the Christmas Club—"all paid for in advance." This of course has culminated in the problem of over-utilization and its foreseeable counteraction—that of governmental demand for com-

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minnesota medicine

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Hemolysis Associated with Intracardiac Prostheses

Diagnosis and Management

REX B. SHAFER, M.D.*
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Minneapolis, Minnesota

HEMOLYTIC ANEMIA is a recognized complication of cardiac surgery. Two types have been described: first, a mechanical hemolytic anemia associated with repair of septal or atrioventricular canal defects,[1-4] and with valvular replacement with an intracardiac prosthesis;[5,6] and second, a type of hemolytic anemia associated with valve replacement, which is thought to be on an auto-immune basis.[7]

The purpose of this report is to illustrate the character and mechanism of the mechanical hemolysis associated with the use of the Starr-Edwards aortic valve in two patients, one of whom was anemic. The diagnosis, conservative management, and effect of exercise is described.

Case Reports

Case 1

A 38-year-old male had acute rheumatic fever with carditis in 1945. Excretional dyspnea began in 1961 and acute congestive heart failure in 1964. The predominant valvular lesion was aortic insufficiency. A Starr-Edwards aortic valve prothesis was inserted in September 1964. Postoperatively, the patient did well except for complaints of recurrent anterior chest pain. No diastolic murmur was present. His laboratory evaluation was completely normal, including hemoglobin and reticulocyte count.

In August 1965 he was evaluated for "cardiac neurosis." The physical findings were unremarkable other than for a Grade 3/6 precordial systolic murmur with a characteristic prosthetic "click." No diastolic murmur was heard. There was no hepatosplenomegaly or findings of congestive heart failure. The hemoglobin was 14.5 g/100 ml. Special hematological studies indicated chronic hemolysis (Table).

Case 2

In 1958 a 42-year-old male farmer was found to have a cardiac murmur of aortic stenosis on evaluation of exertional chest pain. There was no history of rheumatic fever. In October 1964, despite prior restriction of activity, he began to have severe orthopnea, exertional dyspnea, palpitations and syncopal episodes. In January 1965 cardiac catheterization studies confirmed the presence of aortic valvular stenosis (a systolic gradient of 60 mm of mercury) with minimal regurgitation. A Starr-Edwards aortic valve prosthesis was inserted on March 10, 1965. The postoperative course was uneventful. No diastolic murmur was initially described. Preoperatively the hemoglobin was 16.1 g/100 ml. Five blood transfusions were given following surgery to raise the low postoperative hemoglobin. Four weeks after the operation, the hemoglobin was 11.9 g/100 ml; the reticulocyte count, 10.5 percent.

---

*Department of Medicine, Veterans Administration Hospital and the University of Minnesota Medical School, Minneapolis, Minnesota.

Fourteen weeks after the operation the patient complained of increasing fatigue, shortness of breath, and "pounding" in his chest with the slightest exertion; and his urine was persistently dark. Physical examination revealed pallor. A grade 3/6 precordial systolic murmur with a prosthetic "click," and a grade 2/6 mid-diastolic murmur along the left sternal border were noted. The latter was thought to represent aortic regurgitation. Cardiomegaly, a palpable thrill over the aortic area, and a wide pulse pressure were also present. The hemoglobin was 6.7 g/100 ml and the reticulocyte count, 6 percent. Oral iron therapy was instituted and continued until May 1966, but anemia persisted because of continuing hemolysis. At this time he was again hospitalized for the severe anemia and refractory congestive heart failure.

The patient was readmitted to the hospital in March 1967 because of progressive weakness, loss of appetite, easy fatigability and persistence of dark urine. (Hematological evaluation indicated a severe hemolysis (Table). Demonstration of aortic insufficiency clinically and by angiography was the indication for surgical repair of the leak around the prosthetic aortic valve. The leak was due to prosthetic cuff separation in the area below the left coronary artery near the sinus of Valsalva. This was repaired with a 2-0 Tevdek suture and Ivalon sponge. The patient's postoperative course was uneventful. A postoperative hemoglobin was 13.6 g/100 ml. One year after surgery a compensated hemolytic state was documented. The hemoglobin was 14.0 g/100 ml, and multiple reticulocyte counts averaged 4.5 percent.

Results

A summary of the hematological data on the two patients, as well as a comparison with similar data reported by Sears and Crosby[8] in 1965, is found in the Table. A majority of the tests were abnormal for Patient 2.

Increased Fragmented Red Cells

The hemolytic process is characterized by an increased number of fragmented red blood cells in the peripheral smear. Reticulocytosis was present to a significant degree and haptoglobins were absent. Methemoglobinemia indicates red blood cell destruction and overloading of the haptoglobin system. Excess iron was present in the urine. Both direct and indirect Coombs' tests were negative.

Shortened Survival Time of Red Cells

Even though iron was being lost in the urine, the serum iron was normal, as was the iron-binding capacity. Bone-marrow iron, a more sensitive measurement of body iron stores, reflected the urinary iron loss. Fecal urobilinogen from red blood cell destruction was elevated. Chromium^{51}-tagged red blood cells from the patient and from a normal healthy donor showed shortened survival times indicating an extra corpuscular mechanism of cell destruction. Bone marrow examination showed increased erythroid activity.

Patient 1, who was thought to be asymptomatic, did in fact have a mild though compensated process characterized by reticulocytosis, absent haptoglobins and increased urinary heme pigments. These observations point to an extra corpuscular mechanism in the production of the anemia. This process was accentuated by exercise and was associated with significant iron loss.

Patient 2, who was symptomatic, had definite evidence of erythrocyte destruction by an extra-corpuscular mechanism. This hemolysis was characterized by increased reticulocytes, presence of fragmented red blood cells in the peripheral smear, methemalbuminemia, absent haptoglobins, increased fecal urobilinogens, hemosiderinuria, and markedly shortened red blood cell T/2 survival time.

Other Factors

In a 1965 report by Sears and Crosby,[8] hemolysis with anemia appeared in one patient after repair of an ostium primum defect and in another, following replacement of a damaged aortic valve with a Starr-Edwards prosthesis (Table). Their first patient had a striking pattern of diurnal hemoglobinuria; their second patient showed a relationship between physical activity and rate of hemolysis.

In an attempt to show this relationship in our patients, each was exercised by walking down six flights of stairs. Measurement of plasma heme pigments before and after exercise, as seen in the Table, showed an elevated resting level and a significant increase with exertion in Patient 2. Though there was measurable urinary hemoglobin in both patients, indicating increased hemoglobin excretion, there was no significant day/night variation.

Discussion

Hemolytic anemia following the insertion of an intracardiac prosthesis was first reported in 1955 by Sarnoff and Case.[9] Severe hemolytic anemia developed in dogs following the insertion of a Hufnagel valve into the thoracic aorta. The anemia was characterized by hemoglobinemia, hemoglobinuria, hemosiderinuria and a greatly shortened red blood cell survival time. The hemolytic process apparently resulted from mechanical trauma to the red cells when the rigid ball was forced against the rigid housing. When an elastic silicone valve with a more resilient housing was used, a substantial reduction in red cell destruction was noted.

Hemolytic anemia, as a complication of an intracardiac prosthesis, was first described by Sayed and his associates in 1961.[1] A patient, with an ostium-primum defect repaired with a teflon patch, developed anemia, reticulocytosis, hemoglobinemia, methemalbuminemia and fragmented red blood cells postoperatively. Studies of this patient suggested that the hemolysis resulted from mechanical conditions in the heart, presumably from a regurgitant jet of blood through the cleft mitral valve being driven against the bare teflon patch. The cleft in the valve was repaired and the patch covered with endothelium at surgery. The hemolytic anemia disappeared. Whether the presence of the teflon alone, the lack of an endothelial covering over a roughened surface, or the turbulence of the blood caused the hemolysis could not be determined. Possibly all three factors were involved.

Additional reports of hemolysis associated with patch repair of septal and atrioventricular canal defects came from Verdon and associates and from Sigler and his co-workers in 1963.[2,3] In each patient an iron deficiency developed, probably related to the continued hemoglobinuria. In each individual, a persistent defect in the mitral valve permitted a jet of blood to strike the bare side of the teflon patch. Correction of the defect resulted in abrupt cessation of hemolysis.

Sanyl and his group, in 1964, described a case of hemolytic anemia following closure of an ostium-primum defect.[4] They were able to

TABLE

Hematological Data	Patient 1	Patient 2	Sears & Crosby (8)	Normal Range
Fragmented cell (%)	0.4-0.5	7.3-8.8	4.5	<0.8
Reticulocytes (%)	1.4-3.2	4.7-9.2	8.0-9.0	0.5-1.8
Methemalbumin (Shumm's test)[12]	Negative	Positive	Positive	Negative
Hemosiderinuria	—	Positive	Positive	None
Coombs' test	Negative	Negative	Negative	—
Haptoglobin (mg%)	Absent	Absent	Absent	30-180
Serum iron (mcg%)	97	78	54	55-175
Iron-binding capacity (mcg%)	275	221	389	222-400
Fecal urobilinogen (mg/24hr)	285	445-980	—	20-280
Sequestration-Spleen/Liver (Chromium 51 tagged RBC)	Negative	Negative	—	—
Red cell survival time (days)				
Patient cells into patient	25	13	13	24-31
Donor cells into patient	—	11	—	—
Bone marrow	—	Erythroid hyperplasia	Erythroid hyperplasia	— —
Bone marrow iron		Decreased	Decreased	
Plasma heme pigments (mg%)				
Resting	3	46	35	<5mg
Exercise	3	52	43	<5mg
Urinary hemoglobin (mg/hr)	Day .03 Night .04	Day .08 Night .06	None None	None None

maintain their patient in a compensated state by blood transfusions and iron replacement. These authors felt that vigorous medical management was indicated because of the high mortality associated with reoperation.

Hemolytic anemia following insertion of a Starr-Edwards ball valve was first reported by Stevenson and Baker[5] and by Marsh,[6] in 1964. Four patients developed a hemolytic anemia after insertion of a Starr-Edwards valve for correction of aortic valvular disease. In these cases, the postoperative course was complicated by aortic insufficiency. These writers concluded that recognition of hemolytic anemia following prosthetic valve surgery was important because it indicated the operation had not been completely successful.

Reed and Dunn in 1964 demonstrated that aortic insufficiency alone was not a requisite in the development of hemolytic anemia.[10] At necropsy their patient did not have any anatomical evidence of aortic insufficiency; instead, there was obstruction to blood flow in the aorta during systole when the ball was in the open portion of the cage. This allowed little clearance around the ball, and the resultant turbulence was probably a major factor in hemolysis.

In a somewhat similar patient described by Garcia et al. severe hemolytic anemia developed in the absence of aortic valve insufficiency, over a two-year period following surgery,[11] and could not be controlled by medical management. The prosthesis was therefore replaced by a homograft aortic valve. The silastic ball component of the Starr-Edwards valve was found to be enlarged, roughened, and coated with lipids, thus obstructing blood flow through the valve. This enlargement resulted in restriction of free movement of the ball within its cage and probably led directly to the mechanical hemolytic anemia. Several months after the insertion of the homograft valve the patient had normal blood parameters, as well as return of cardiac function to a near normal state.

Certain diagnostic tests are important to detect hemolysis in a patient following cardiac surgery. The peripheral blood smear will show fragments of red blood cells, poikilocytosis, and anisocytosis and polychromasia. The red blood cells may also reflect chronic iron deficiency. The hemoglobin and hematocrit will be correspondingly low. The reticulocyte count will be elevated, even in the face of a normal or near-normal hemoglobin. The detection of hemosiderin in the urine is important in documenting chronic iron loss. Plasma haptoglobins are absent and plasma hemoglobin is increased. The presence of methemalbumin in the serum is diagnostic of a hemolytic process, as is the presence of increased fecal urobilinogen. Measurement of serum iron and iron-binding capacity may frequently reflect the chronic iron loss.

The evaluation of iron in the bone marrow is a more sensitive measurement of reduced body iron stores. These stores may be decreased when the serum iron is still within a normal range. The number of normoblasts in the bone marrow, reflecting erythroid hyperplasia, should also be noted. Both the direct and indirect Coombs' are usually negative except for those rare instances of "auto-immune" hemolytic anemia, an example of which was reported by Pirofsky et al.[7] Measurement of chromium^{51}-tagged red blood cell T/2 survival time will show a decrease in the patient's own cells as well as in normal donor cells circulating in the patient. Body scanning for sequestration of labelled red blood cells is usually not helpful. In cases where this has been done, there has been no selective sequestration in the liver or spleen. Measurements of osmotic and mechanical fragility are usually normal, as are tests for antibodies, including cold agglutinins, cold hemolysins, and acid hemolysins. Hemoglobin electrophoresis and red blood cell metabolic studies have been similarly normal or negative.

Conservative management is usually the best initial approach with these patients. Successful compensation has been reported with the use of multiple transfusions, steroids, iron replacement and, in one instance, auto-transfusion. The possible value of limitation of physical activity should be considered in some patients. Uncompensated hemolytic anemia, alone, or associated with persistent valve insufficiency or recurrent left to right shunt, may be an indication for reoperation.

Summary

Chronic hemolysis was documented in two patients with Starr-Edwards aortic valve prostheses. Diagnosis was suspected from find-

ings of fragmented red blood cells in the peripheral smear and an increase in the number of reticulocytes. The process was further demonstrated by a shortened chromium^{51} T/2 survival time, decreased serum haptoglobins, increased plasma heme pigments and increased urinary hemosiderin excretion. The process was accentuated by exercise and associated with significant iron loss.

Conservative management in symptomatic patients may require transfusions, iron replacement, and restriction of physical exercise. Persistence of an uncompensated anemia is often an indication for reoperation.

Acknowledgments

We are indebted to Donna H. Ripley, Special Hematologist, Special Hematology Laboratory and Marija B. Feders, Research Technologist, Minneapolis Veterans Administration Hospital, for the special hematology studies on these patients.

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Medicine in the Middle Ages

Mention should also be made of that famous medieval surgeon, Guy de Chauliac, who studied medicine at Toulouse, Montpellier, Paris, and Bologna—a record that should encourage students who don't make it the first time. He was immensely learned, especially about medical schools. The most memorable thing about Guy is his having been probably the first to employ traction in the treatment of a fracture. Anyone with a broken thigh who has been ingeniously trussed up with ropes, pulleys, and weights until he looks like a spider weaving a web should thank Guy de Chauliac and not Rube Goldberg.*

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*Richard Armour: It All Started with Hippocrates, 1966.

Worry

There are two days in every week about which we should not worry. One is yesterday, with its mistakes and cares, its aches and pains. Yesterday has passed forever beyond our control.

The other day is tomorrow, with its possible adversities and blunders. Until its sun rises we have no stake in tomorrow, for it is as yet unborn.

That leaves only one day—today. Any man can fight the battle of just one day. It is only when we add the burden of those two awful eternities—yesterday and tomorrow—that we are liable to break down.*

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*Illinois Medical Journal.

FEATURE SPECIAL

Medical Terms and Their Lay Synonyms

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There is no doubt that scientific nomenclature has its advantages. It predisposes to exactness and usually pinpoints objects with remarkable accuracy. Its preciseness requires that the user understand it as well as the listener. This language is supposedly only denotative, but through common usage has taken on a connotative value within the scientific professions.

Unfortunately, to the average man scientific language is but a conglomeration of Latin and Greek endings preceded by even more weird beginnings. This is perhaps most notable in medical jargon where the doctor's vocabulary consists of "oses" and "itises" and the patient speaks of aches and pains. This is fine when patients talk to patients and physicians consult among themselves; but when doctor and patient meet there are usually, if not always, problems of communication. In most cases these are resolved by repeated questioning and constant probing by the doctor into the patient's complaints—to the point of sheer boredom and needless repetition. In some instances the doctor never learns what the patient's problems are; in other cases the patient tells the doctor what he wants to know regardless of its bearing on the truth. These two consequences are certainly anything but satisfactory.

It goes without saying that the problems of communication ever present between physician and patient deserve resolution. As it would be quite impossible to teach the myriad of lay people the meanings of medical expressions and how and when to use them, it behooves us doctors to learn, appreciate, and understand those expressions, those disease names, those conditions, those flagrantly false and nonsensical terms patients use.

Included here is such a list.

The list is certainly not comprehensive but is, however, fairly accurate. Some of the definitions appear contradictory, others incomprehensible; many of the terms are obsolete, others quite up-to-date. Most of them are American if not English. Some you have used yourself. Others you will never see again.

These 1500 words are just the beginning of a list that has no ending, for people are always devising new ways to describe things. It is impossible to learn them all, but it would be nice to know a few of them. Besides they make great fodder for one-upmanship!

A

ABC—*abscess*
Abortion fever—*brucellosis*
Abortus fever—*brucellosis*
Absorbants—*lymph vessels*
Achecorns—*sore feet*
Achilles heel—*tendon of gastrocnemius*
Acid-fast resort—*tuberculous sanitarium*
Acute anemic dropsy—*thiamine deficiency*
Acute rheumatism—*rheumatic fever*
Adam's apple—*prominentia laryngia*
Alvine concretions—*intestinal calculi*
American Q fever—*Q fever*
Ammas—*alistrim*
Amog—*hysteria*
A mother's duty—*menstruation*
Amuch—*hysteria*
Anatomist's wart—*verruca necrogenia*
Angina externa—*parotitis*
Anginaparotidea—*parotitis*
Angina plastica—*diphtheria*

(To be continued next month)

Anesthesia after Myocardial Infarction

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Arteriosclerosis of the coronary arteries is the leading cause of death in this country. According to a national health study, 2.8% of all adult males between 18 and 70 years have coronary heart disease, and an additional 2.5% are suspected of having it.[1] This survey also revealed that 23.6% of all men who have angina pectoris have had myocardial infarction. As a result, the number of patients with coronary artery disease undergoing some form of surgery is increasing steadily. These patients present problems related to the specific physiologic changes caused by their pathologic condition. A special group consists of those patients who must be subjected to the stress of anesthesia and operation during the early postinfarction period, with a resulting higher mortality rate.[2]

The Surgical Risk

Optimal Time

The optimal time to operate on a patient who has had myocardial infarction is by far the most important facet of this problem. Usually healing is complete within three months, depending on the size of the infarct and the condition of the myocardial circulation.[3] Most infarcts require about two months to establish vascularized scar tissue and perhaps another month to consolidate the recovery. Thus the extremely critical period probably extends over two months. This concept is supported by statistical data. In a study by Arkins and associates,[2] among 27 patients with recent infarction (less than three months), 11 died during or after operation (40%); yet, in a group with old myocardial infarction (more than three months), only 54 of 240 patients died (22%).

High Mortality

In a study by Fraser and associates,[4] the overall mortality rate was 38% for patients with recent infarction and particularly high for patients who underwent operation within 15 days after myocardial infarction. Of 28 patients operated on during this interval, 12 died (43%).[4] However, only six of these deaths were related to the cardiac disease. Associated diseases that necessitated operation were considered the direct cause of the other deaths. The mortality rate decreased for those operated on after 15 days. The impression was that judicious delay of operation in all but the most urgent situations was indicated during this period because prognosis seemed to be better if operation took place after the first 15 days.

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*Mayo Clinic and Mayo Foundation: Section of Anesthesiology.

Location of the Infarct

The type of infarction was also found to be significantly related to the outcome. In the study of Arkins and co-workers,[2] 13 patients had recent anterior and posterior wall infarction (transmural) and 14, subendocardial infarction. Ten of the 13 with transmural infarction died, but only one with a subendocardial lesion died. According to this study, there was no significant difference after operation between the mortality rate of patients with old infarction and those with other coronary changes without infarction (mortality rates of 22% versus 21%).

Location of the myocardial infarct is of special interest to the anesthesiologist, especially during operation. Anterior infarcts result from occlusion of the anterior descending branch of the left coronary artery.[5] Because this artery does not supply the sino-atrial or the atrioventricular node, heart block is uncommon. Hence, rhythm and conduction defects are unlikely with anterior infarction; yet an extensive infarct may cause congestive heart failure. Lateral infarction results from occlusion of the left circumflex coronary artery,[5] which has a variable distribution. If the sinoatrial node or the atrioventricular node is supplied by this artery, serious arrhythmias or heart block can be expected. A posterior infarct results from occlusion of the right coronary artery,[5] which regularly supplies both of these types of nodes, and these patients are most likely to have disturbances of rate and rhythm.

Preoperative Considerations

The aim of any anesthetic technique is to provide a state in which the surgeon can operate with as little physiologic and emotional trauma to the patient as possible.[6] In this respect, anesthesia for the patient with cardiac disease is not different in kind but only in degree.

Cardiac Stability

It is important to determine the state of cardiac reserve and the stability of the cardiac status. A careful history, physical examination, and preoperative electrocardiogram should identify the presence of previous myocardial infarction or coronary insufficiency. It is also important to make sure that the changes are not due to a recent infarction. If the infarct is recent, elective surgery should be postponed as long as possible, preferably beyond the three-month healing period.

Patients with signs of coronary insufficiency, cardiac enlargement, congestive heart failure, cardiac arrhythmias, or pulmonary diseases should be adequately prepared before operation by appropriate medical treatment. This ensures that the patient is brought to the operating room with the best possible cardiac compensation.[7]

Prophylactic Digitalization

Preoperative preparation should include prophylactic digitalization in patients who have cardiac failure or impaired reserve, treatment of anemia by proper measures, and regulation of fluid and electrolyte balance. In patients who have been receiving prolonged digitalis and diuretic therapy, total-body potassium is likely to be reduced; that is, a significant reduction of intracellular potassium may be present without a change in the serum potassium level and may cause hyperirritability of the myocardium, with ventricular ectopic rhythms.[6] One rational treatment is to give potassium chloride intravenously; another is to depress the ectopic foci with diphenylhydantoin or lidocaine.

Sedation

Tachycardia of emotional origin should be avoided by reassurance and adequate sedation.

Effective doses of sedative drugs are safe and most worthwhile to relieve the anxiety of the patient who is to undergo operation. Morphine has a specific place because it has a calming effect, may relieve the pulmonary congestion by allowing peripheral pooling,[8] and may improve ventricular performance.[9] Belladonna drugs given before operation may prevent vagal bradycardia, but if this occurs it can be treated effectively by small intravenous doses of atropine when needed. Another effective drug for premedication is meperidine. The small decrease in arterial oxygen tension that is seen when this drug[10] is used also occurs after morphine, but the decrease can be easily counteracted with an increase of inspired oxygen tension.

Considerations During Operation

The principles are: (1) maintaining light anesthesia, (2) assuring satisfactory ventilation (usually by controlling it) with adequate oxygenation, (3) abolishing vagal stimulation, and (4) avoiding serious arrhythmias and hypotension. Our experience is that the patient with impaired circulatory system tolerates even less depression than does the patient without such impairment. Thus all efforts are directed at maintaining the circulation. Fortunately, the cardiac patient who can tolerate only a light level of anesthesia usually needs no more than that. Equally important is the realization that the patient with an extremely low cardiac output can maintain a reasonably stable blood pressure if given light anesthesia with ample oxygen.[6] As is true in so many circumstances, it does not matter what you use but how well you use it. The choice of anesthesia depends on one's preference and experience in relation to what is safest for the patient's condition.

Almost every anesthetic agent has a depressant effect on the myocardium in deeper levels that decreases cardiac output. The myocardial depressant effect of halothane is well tolerated in light levels of anesthesia.[11] Hypoxia and especially hypercapnia have an important part in the initiation of arrhythmias. In general, hypoxia does not often cause arrhythmia in the normal heart; but if the patient has coronary heart disease, ventricular arrhythmias easily result because of enhanced excitability of the hypoxic areas of the heart muscle.[12] Hypercapnia also provokes ectopic rhythms.

Ventilation

It has been established clinically that retention of carbon dioxide during halothane anesthesia causes various arrhythmias of ventricular origin.[12] Hypoxia can be due to laryngeal spasm, hypoventilation, ventilation-perfusion abnormalities, and pulmonary shunting (which occurs particularly during thoracic surgery). Arterial oxygen tension can decrease to dangerously low levels even when the patient is ventilated with 100% oxygen, because of pulmonary shunting.[13]

Hypotension

Avoiding a decrease in blood pressure probably is the most important single factor in the safety of the patient during operation. If a decrease does occur, the cause should be determined and treatment given immediately. Hypotension will cause a reduction in coronary blood flow, leading in turn to myocardial hypoxia, with reduced cardiac output and further decrease in blood pressure.[14] Therefore the importance of detecting even transitory bouts of hypotension is apparent.

Monitoring

Since the prompt recognition of changes during anesthesia is critical for the patient's prognosis, monitoring of several variables is mandatory. This includes the use of the electrocardiogram and the monitoring of the heart rate and tones by stethoscope and of the blood pressure by cuff or even by direct reading with a pressure transducer. Also the capability to do serial analyses for oxygen, acid-base balance, and electrolytes during or after operation for these high-risk patients adds greatly to the safety of the procedure.

Postoperative Considerations

The incidence of myocardial infarction after operation is probably higher than is generally suspected. Arkins and associates[2] reported that 5% of the 1,005 patients with coronary artery disease had myocardial infarction after operation. Patients with recent myocardial infarction are exposed to a greater risk of recurrent infarction,[7] and the mortality rate for patients with recurrent infarctions is high. In one series, three patients who had recent infarction before operation died from recurrent postoperative infarction. In the same study, 18 patients with old myocardial infarcts also had recurrent postoperative infarcts, and 14 died (77.7%).[2]

Hemodynamic disturbances such as tachycardia, hypotension, and lowered cardiac output are the responsible factors for the infarct.[7] Hypoxemia also occurs to some degree after general anesthesia and every operation. Arterial oxygen tension decreases on the second and third postoperative days, when the patient is breathing air, because of miliary atelectasis.[15] This period of hypoxemia corresponds well with the occurrence of more than half of the observed myocardial infarcts during the first three postoperative days.[7] The finding that all patients, not only those with heart disease, require treatment of lowered arterial oxygen tension needs wider appreciation by those involved in anesthesia and surgery. A corollary here is the necessity for giving oxygen to patients after operation and for making vigorous efforts to reduce atelectasis, such as encouraging frequent coughing and deep breathing and turning the patient, as well as the use of intermittent positive-pressure breathing.

Summary

The mortality rate for patients with recent myocardial infarction is high if they are submitted to the stress of anesthesia and surgery. Elective surgery should be delayed until after a healing period of three months. Patients should be prepared and brought to surgery in the best possible state of cardiac compensation. Management of the patient during the operation includes a light level of anesthesia, adequately controlled ventilation and oxygenation, and abolition of undesirable vagal reflexes. Monitoring must be sufficient to provide adequate knowledge of the dynamic status of the patient. Hemodynamics must be carefully observed and corrected or supported as needed.

Postoperative myocardial infarction is frequent and is associated with a high mortality rate. Patients with coronary artery disease should be kept under constant surveillance after the operation. Hypoxemia commonly occurs after anesthesia, requiring treatment with oxygen and vigorous efforts to reduce atelectasis.

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Better do a little well, than a great deal badly.—Socrates.

Hepatic Coma in Pregnancy

Treated with Exchange Transfusion

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There have now been about 82 cases of fulminant hepatic coma secondary to infectious hepatitis and other causes treated by exchange transfusion.[1] Since the evaluation of this treatment is still in its early stages, we felt it was necessary to include another case in the literature. This case also is unique in that the subject was a young pregnant female. There has been one other pregnant woman with hepatic failure successfully treated by exchange transfusion.[2] The diagnosis of this reported case was fatty change of the liver associated with the third trimester of pregnancy.

Report of a Case

History and Physical Examination

An 18-year-old white female was admitted to the obstetrical service after the abrupt onset of nausea, vomiting and abnormal pain three days prior to admission. She was 20 weeks pregnant. Four days prior to admission she had seen her private doctor, who diagnosed a urinary tract infection and started her on methenamine mandelate (Mandilamine) and phenazopyridine hydrochloride (Pyridium). Associated with this medication, her urine became orange in color. She was also taking an iron and vitamin preparation. There was no history of blood transfusions, tranquilizing drugs, tetracycline or infectious hepatitis. No history of exposure to narcotics, amphetamines or methadrine was elicited. Past medical history included one previous pregnancy terminating in a live birth and accompanied by an episode of cervicitis.

Physical Findings

Physical examination revealed an icteric, somewhat drowsy female who responded appropriately to questions. Other positive findings included nystagmus to all quadrants and a moderately loud systolic murmur at the left sternal border. The liver edge was at the costal margin and tender. The uterine fundus was at the level of the umbilicus. No other neurological abnormalities were observed.

Laboratory Data

Initial laboratory studies found a hemoglobin of 12.8 Gm%, a white blood count of 18,200 with 84% neutrophils. Urinalysis showed 1+ albuminuria and 10-12 wbc/hpf. The prothrombin time was 39.2 seconds with a control of 12.6. The initial SGOT was over 250 units but, unfortunately, the serum was not diluted. The following day the SGOT was greater than 750 units, and again dilutions were not carried out to yield the exact value. The total bilirubin was 10.2 mg% with 44% direct-acting. The alkaline phosphatase was 29 King-Armstrong units. The CO_2 was 9 mEq/L while the other serum electrolytes were normal. A cephalin flocculation was 4+ and thymol turbidity 20 units. A lumbar puncture was traumatic but otherwise negative. The tentative diagnosis of infectious hepatitis was made.

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Hospital Course

On the evening of admission the patient was treated with parenteral vitamin K, 5% dextrose solution containing sodium bicarbonate, potassium and sodium chloride; penicillin and chloramphenicol (chloromycetin) were also administered. Twelve hours after admission she became restless and by eighteen hours after admission she had become comatose. Neurological examination showed dysconjugate gaze, pupils midposition and reactive to light, decerebrate rigidity with positive Babinski reflexes. Conjunctival hemorrhages were present. A carotid angiogram was negative.

Exchange Transfusion

Based on the presumptive diagnosis of fulminant hepatic coma secondary to infectious hepatitis it was elected to perform an exchange transfusion. Ten units of citrated blood, less than five days old, were exchanged. Twelve hours following the first exchange transfusion the decerebrate posturing had disappeared. Two more exchange transfusions were done 48 and 72 hours after the first exchange. In the latter procedures nine and ten units of freshly-drawn heparinized blood were used respectively. Twelve hours after the last exchange transfusion, the patient began to respond and by 24 hours she was entirely awake. During the period of coma, hydrocortisone sodium succinate (Solu-Cortef) was continuously administered up to a dose of 1.0 Gm. per day. Neomycin sulfate was administered by means of a nasogastric tube following tap water enemas.

Further treatment following the period of coma included prednisone 30 mg. per day in divided doses, which was continued and finally tapered and discontinued on the 50th hospital day. A high caloric diet with slowly increasing protein was administered. On the day she became conscious she began to show a pneumonitis with staphylococcus and pseudomonas, which was treated with sodium cephalothin (Keflin) and sodium colistimethate (Coly-Mycin). On the 21st hospital day she aborted an 800-Gm. fetus which had been alive right up to the delivery.

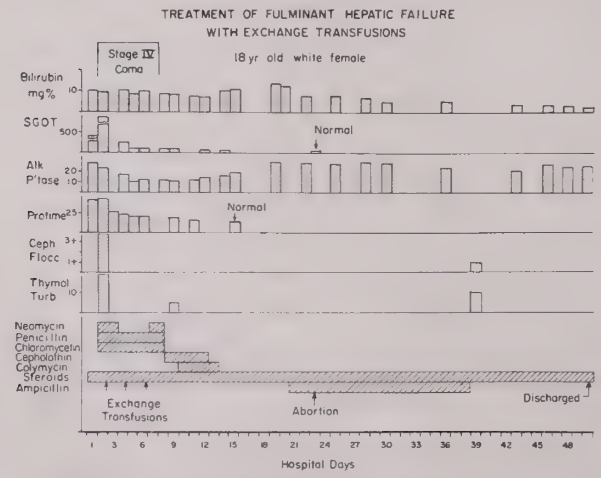

Fig. 1—The pertinent laboratory values during the hospital course of a young pregnant female with fulminant hepatic failure.

Summary of the pertinent laboratory results during the hospitalization appears in Figure 1.

Pathology

Liver biopsies were done on the ninth and 46th hospital day. The first specimen showed marked bile plugging of canaliculi, bile stasis, ballooning degeneration and areas of pericholangitic inflammation with polymorphonuclear infiltration (Figures 2 and 3). The later specimen showed bile thrombi in the canaliculi and partial resolution of the earlier changes (Figure 4). The changes seen in the biopsy were not entirely typical of infectious hepatitis; however, the effect of the pregnancy and the

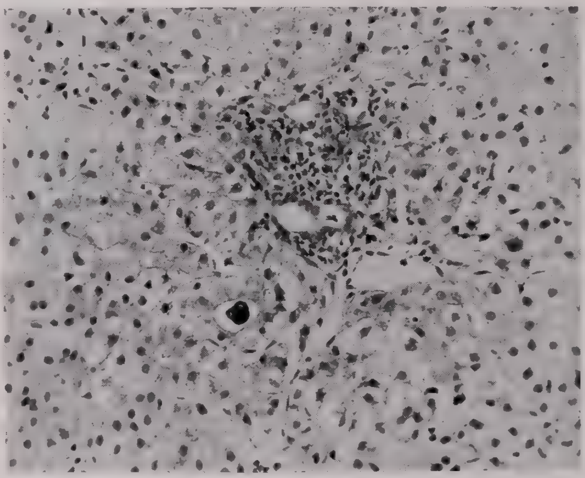

Fig. 2—A liver biopsy specimen from the ninth hospital day of a 18-year-old female with fulminant hepatic failure. Bile stasis and acute pericholangitis can be seen. Magnification 240x.

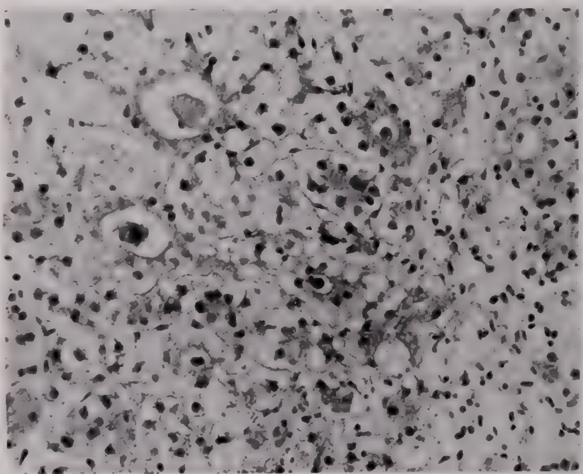

Fig. 3—Another area from the first liver biopsy with ballooning degeneration and demonstrating disordered architecture. Magnification 240x.

large doses of steroids on the liver must be taken into account in interpreting the microscopic changes. Considering all the data, the most likely diagnosis would seem to be viral hepatitis. The architecture of the aborted fetus liver was normal. The patient was discharged after 50 days of hospitalization. She is well five months later.

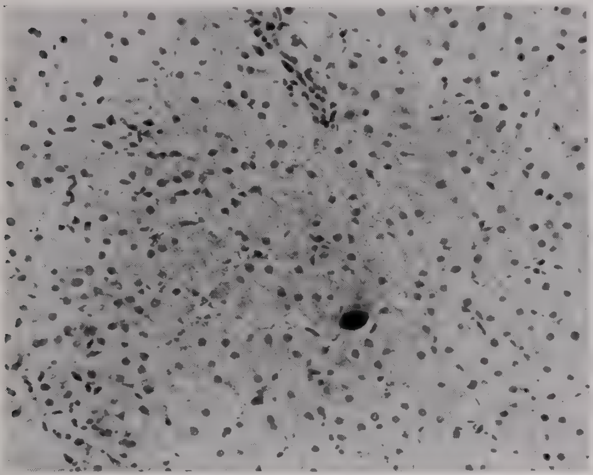

Fig. 4—A repeat liver biopsy specimen on the 46th hospital day showing residual bile plugging and improvement. Magnification 240x.

Discussion

The cause of the fulminant hepatic failure in this case was not entirely clear since the liver biopsies did not indicate the usual pattern of parenchymal cell necrosis seen in infectious hepatitis. However, the structural picture, mostly of the cholestatic type, may have been remarkably altered by massive steroid therapy and pregnancy.

Recurrent jaundice of pregnancy would seem to be an unlikely etiology in this case. In a series of Danish patients with jaundice in pregnancy, 75% of the cases were said to be recurrent jaundice of pregnancy, while 17% were viral hepatitis.[3] The abnormal cephalin flocculation, thymol turbidity, and bilirubin levels in our patient are not consistent with this diagnosis.[4] The thymol turbidity is generally normal in recurrent jaundice of pregnancy, while bilirubin is said not to be a greater than 8 mg %. Viral hepatitis in pregnancy has been reported in India to have an extremely grave prognosis.[5] Western authors do not indicate such a high mortality[4] and attribute the Indian result to poor nutrition.

The first series of patients treated by exchange transfusion were those of Trey et al.[6] There have since been about 80 cases treated in this fashion[1] and some modifications have been presented, such as the use of plasma exchange.[7]

The survival in this case of fulminant liver failure was unexpected, and one would like to attribute it to the vigorous treatment. However, there were three modes of therapy combined: standard hepatic coma therapy, steroids, and exchange transfusion. It is therefore not possible to consider this case solely as evidence supporting the value of exchange transfusion. In a recent report Davis et al.[8] indicated that exchange transfusion was no better than conventional treatment in cases of fulminant viral hepatitis. In their series 37% of 16 patients survived with conventional therapy including steroids. Of the six survivors two are described as having decerebrate rigidity during the coma period.

In contrast to the remarkable recovery rate of Davis, only 17.4% of 207 cases reported in the literature from 1951 to 1967 and summarized by Burnell et al.[9] survived massive hepatic necrosis after viral hepatitis with conventional treatment and steroids. These authors collected their cases from 14 separate reported series ranging from two to 26 cases each. If one computes the standard deviation of these series using a weighting factor* to emphasize the larger series one discovers that one standard deviation (18.6%) would encompass the range 0% to 36% recovery. One cannot then conclude from one small series the efficacy or failure of treatment. Obviously many more cases are needed. More recently a cooperative study report shows about a 22% survival in all cases of fulminant hepatic failure compared to 10% in the non-exchange group.[1] This study had, at the time of the report, 150 individuals; however, the difference between those exchanged and not exchanged was not statistically significant.

Summary

A pregnant woman with fulminant hepatic failure was successfully treated by exchange transfusion coupled with conventional measures.

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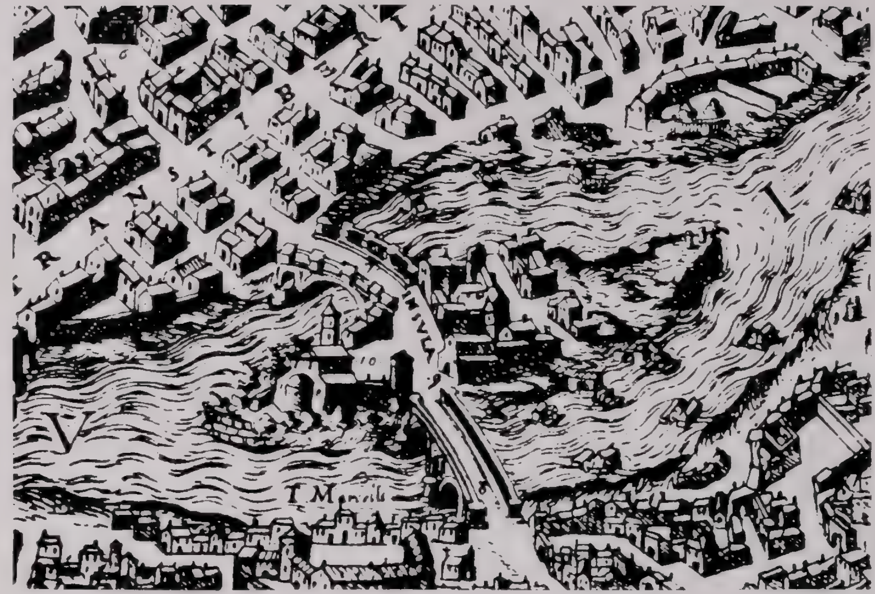
*Snedecor's Statistical Methods, Iowa State College Press, 5th edition, Page 500.

References can be secured from the author or the reprints.

FEATURE SPECIAL

Old Hospitals



The Ship in the Tiber from an engraving dated 1577

The Ship of Aesculapius

During an epidemic about 293 B.C., the Romans adopted the Greek god of medicine, Aesculapius, as one of their major deities, and they erected to him a great temple on this island in the Tiber. They imported physicians and Aesculapian serpents from the great Greek medical center at Epidaurus, and made the island the chief hospital or sanitarium of the city. The island, cut into the shape of a ship 300 yards in length, 80 yards in beam and complete with mast, prow and stern, resembled a huge ship at anchor in the river. Beside the great temple, the island provided smaller satellite temples, shelters for the sick, medicinal baths, and enterprising Romans selling votive offerings on the river bank. During times of pestilence, the location of the medical center on an island provided at least a rudiment of isolation.

Imperial Rome saw the island become a refuge for the sick poor where some men left their ill or worn-out slaves to avoid the trouble of caring for them. The Emperor Claudius (A.D. 41-54) decreed that slaves recovering their health on the island should henceforth be free.

With the coming of the Christian era, the dedication of the island changed, but not the function. A hospice dedicated to St. Bartholomew was built about 1100 A.D., and the Hospital of St. John Calibita in 1575. The latter, now more popularly known as Ospedale Fatebenefratelli, still thrives as a modern 280-bed voluntary hospital.

The island is probably the oldest medical center in the world. Some of the columns which support the Basilica of St. Bartholomew today are said to be part of the original Aesculapian Temple, and down near the island's "stern" one can still make out an Aesculapian staff and serpent carved into the rock by the ancient Romans.

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Coronary Care*

In the Very Small Hospital

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Aggressive management of patients who have suffered an acute myocardial infarction has been well accepted in the large and medium-sized hospitals.[1-4] The very small rural hospitals, however, have not been as quick to accept the challenge, but an occasional very small hospital has overcome the obstacle of smallness, recognizing the importance of immediately available facilities and personnel as contrasted to the risks of transporting an acute myocardial infarction patient long distances to larger centers.[5]

Organization

Plans for establishing an intensive coronary care unit were initiated at the United Hospital in Blue Earth, Minnesota, in early 1967. The hospital is a 40-bed general community hospital serving the city of 4,000 population and the surrounding farm area of 10,000 population. The hospital has a 15-bed satellite unit in the city of Winnebago 12 miles away. The combined staff of the two hospitals is composed of eight private practitioners, all generalists. The radiology and laboratory departments are headed by a visiting radiologist and a visiting pathologist. The staff agreed to the desirability of an intensive coronary care unit and further agreed to admit all patients to the unit with proved or suspected acute myocardial infarction. One member of the staff accepted the responsibility of organizing and operating the unit. A committee was formed to include the physician in charge, the hospital administrator and the director of nursing.

It was recognized that the success of the unit would depend on the competence of the nursing staff; therefore a course of instruction was conducted by the physician in charge, and by visiting physicians and nurses from

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*Read before the Blue Earth Valley Medical Society on April 16, 1969 and read before the annual meeting of the Southern Minnesota Medical Association at Albert Lea, Minnesota, on September 13, 1969, and recipient of the Association's Award for Excellence of Subject Matter and Presentation.

This study was in part supported by the Blue Earth Medical Center, Blue Earth, Minnesota.

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the Mayo Clinic and St. Mary's Hospital of Rochester, Minnesota. Emphasis throughout the course was placed on prevention of cardiac arrest rather than treatment.

Equipment

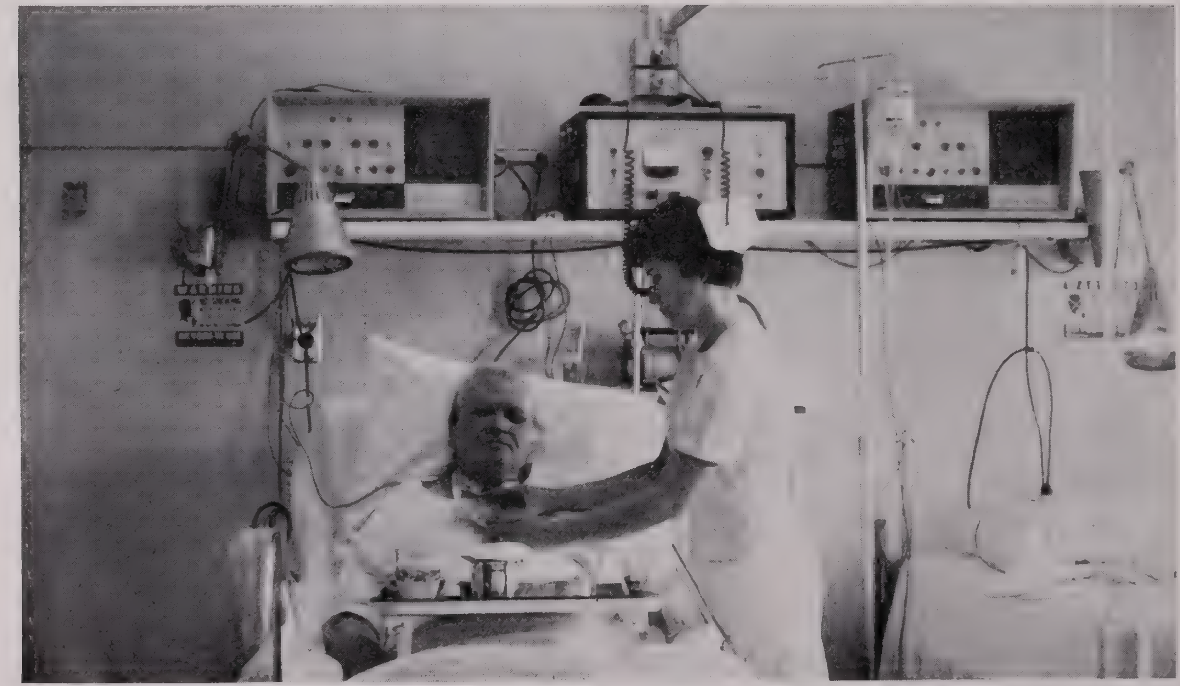
A private room with bath located next to the nursing station was converted to a two-bed unit. A portion of the wall between the room and the nursing station was cut out and replaced with sliding glass to allow constant visual and auditory contact between the station and the patients in the unit. Oxygen was piped into the unit. Each bed had its own overhead monitor-pacer unit. One defibrillator was mounted overhead between the two beds. A remote unit at the nursing station contained two scopes, two rate meters, automatic recording equipment and alarms. Each bed had its own high intensity light source. A third monitor-pacer unit and a second defibrillator were mounted on a portable stand to be kept in the operating room. This portable unit was moved to the x-ray department during insertion of transvenous electrodes and served as a standby unit for use anywhere in the hospital. A small battery-operated portable demand pacer was also available in the unit for transporting and ambulating patients requiring artificial pacing.

Unit Usage and Policy

The unit was designed to provide priority care for patients with acute myocardial ischemia with or without infarction, patients with cardiac mechanism failure or patients with severe congestive failure. However, it was also planned to serve any patient who was critically but not hopelessly ill or injured, including patients in shock or vascular collapse from any cause, including blood loss from severe injury, gastrointestinal and obstetrical hemorrhage.[6] This also included patients with diabetic acidosis, major electrolyte abnormalities, crushing injuries of the chest with myocardial injury or tracheostomies, postoperative patients with critical problems and many other acute problems. Patients in the following categories were excluded from the unit: hopelessly ill, acute alcoholism, psychosis with management problems or ill with communicable diseases.

Patient Management

An intravenous infusion of 5% dextrose and water was started immediately on each new patient. Each patient was then connected to



Figure—Intensive coronary care unit—Blue Earth United Hospital the monitor-pacer by chest electrodes. Oxygen was given to all patients by mask or nasal catheter for at least three days. A list of 32 routine admission orders was used as a check list by the nurse in charge. A reference manual of standard treatment procedures was prepared by the physician in charge and kept in the unit as a guide for the nurses and physicians, to avoid any hesitancy in the treatment of arrhythmias or other complications. In most instances dilute solutions of lidocaine and isoproterenol were connected to the intravenous infusion ready for immediate administration if needed. In some instances a 5-cc syringe of 2% lidocaine was also prepared, to inject as a bolus if indicated for treatment of ventricular arrhythmias.[7] Lidocaine, isoproterenol, quinidine, atropine and propranolol were used with varied frequency. All patients were heparinized immediately and maintained on heparin for at least 24 hours. Long-term anticoagulant therapy was initiated and maintained with warfarin sodium. All patients were encouraged to use the bedside commode and were ambulated early.

External pacing was used very seldom, insertion of the transvenous bipolar catheter electrode was preferred and performed in the radiology department.[8] Routine orders included authority for the nurses to employ any emergency treatment indicated to include counter shock and/or pacemaking.

The Study

All cases showing a final diagnosis of acute myocardial infarction during 1968 were reviewed, this being the first full year of unit operation. The usually accepted diagnostic criteria for a proved myocardial infarction were used, namely: (1) A clinical history of typical pain, (2) classical sequential changes in the electrocardiogram, and (3) a changing elevation of at least one of the three serum enzymes: creatine phosphokinase, transaminase or lactic dehydrogenase. Using the criteria, it was found that a total of 33 proved cases of acute myocardial infarction were admitted to the hospital and treated in the unit during 1968. There were 52 other patients admitted during the year (Table). Some of them had been suspected of having acute myocardial infarction and some were admitted specifically for observation and treatment of previously recognized cardiac rhythm disturbances.

The average length of stay in the intensive coronary care unit for the acute myocardial infarction patients was five days and their hospital stay averaged 15.3 days. No patient was discharged from the hospital until he was ambulatory and free of significant cardiac symptoms.

Results

Mortality

In the group of 33 cases of acute myocardial infarction admitted to the unit during the year, there were six deaths (18%) during the entire hospital stay. These included five women (mean age of 76) and one man (age 84). The mean age of the group was 68. Congestive heart failure accounted for two of the deaths, a cerebral embolism caused one death, rupture of the ventricular wall and pulmonary embolism accounted for another death. The sixth death was due to cardiac asystole. The patient had an AV heart block and was scheduled for insertion of a transvenous pacing electrode, but insufficient urgency was ascribed to the matter and the patient suffered ventricular standstill which did not respond to external pacing. This was probably the only avoidable death in the series. There were no other deaths attributed to cardiac arrest per se.

For comparison's sake, an analysis was made of all cases of acute myocardial infarction admitted to the hospital in 1966, the latest full-calendar year preceding the opening of the coronary unit. It revealed a total of 24 patients with 11 deaths (46%).

TABLE
Type of Patients Admitted to the ICCU

	No. of Patients
Acute Coronary Insufficiency with Proved Infarction	33
Acute Coronary Insufficiency without Infarction	26
Major Cardiac Arrhythmias without Acute Coronary Insufficiency	15
Massive Gastrointestinal Hemorrhage	2
Severe Injuries	4
Diabetic Acidosis and other Medical Illness	5
TOTAL	85

Arrhythmia

Continuous monitoring in the intensive coronary care unit recorded arrhythmias in 31 of the 33 patients. Premature ventricular contractions occurred most commonly: in 30 (90%) of the patients. The most frequently employed anti-arrhythmic drug was lidocaine. External pacing was employed in two patients, both of whom died. Temporary pacing with a transvenous electrode was utilized in four patients, all of whom were ultimately discharged from the hospital in sinus rhythm. Ventricular fibrillation was treated by electroshock in three instances, once unsuccessfully and twice successfully. These procedures were also employed successfully on patients in the intensive coronary care unit during the year on other than those in the acute myocardial infarction group.

Comments

Early intensive coronary care units first established in 1962 have reported a significant reduction in mortality due to myocardial infarction. Compiled statistics of various units reveal a reduction in mortality ranging from 13% to 40%.[1-4] It has been found that the milder cases have a better prognosis for successful resuscitation in the event of cardiac arrest.

Of the total number of cases of suspected acute myocardial infarction admitted to our unit only 50% were subsequently proved to have had an infarction. This means that patients were admitted promptly and without selection. The 46% mortality observed in the 24 cases treated the year before opening of our intensive coronary care unit as compared to 18% mortality during the first year of our unit operation is, in spite of the small size of the series, probably proof enough of the value of the intensive coronary care unit in our small community hospital. Prompt medical treatment of arrhythmias in the intensive coronary care unit and subsequent reduction of the incidence of cardiac arrest may account for this gratifying result. Lown et al. have reported 130 consecutive cases without a single episode of ventricular fibrillation.[3] They attributed this to the change in emphasis from resuscitation to prompt medical treatment of arrhythmias. The ease of pacing the patient with AV block by the transvenous method has also played an important role. More recently pacing has been employed to treat repetitive ventricular arrhythmias.[10]

Conclusions

This study would indicate that the very small community hospital can establish an intensive coronary care unit with a degree of success proportional to the effort and diligence of its personnel and in so doing save lives that would otherwise be lost due to acute myocardial infarction. Moreover, it serves to improve the care to other patients with varying cardiac illnesses. Patients with "mild" myocardial infarction should be admitted to the intensive coronary care unit because the most rewarding results have been observed in this group.

Generic and Tradenames of Drugs

Lidocaine	Xylocaine
Isoproterenol	Isuprel
Propranolol	Inderal
Warfarin sodium	Panwarfin

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He climbs highest who helps another up.—George Matthew Adams.

Prolonged Oxygen Therapy and Mechanical Ventilation

Associated Pulmonary Abnormalities

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Morphologic pulmonary lesions associated with prolonged oxygen therapy and mechanical ventilation have been described.[1-4] As far as can be determined, these changes have not resulted from the disease process that necessitated respiratory assistance; in fact, many patients have not had primary cardiopulmonary disease before the use of assisted ventilation.

In 1966 one of us (J.L.T.) noted that the lungs of patients having assisted ventilation immediately before death showed histologic changes which did not fit into any of the usual categories of lung pathology. Since administration of oxygen or assisted ventilation or both were considered to be etiologic factors at that time, and in view of the recent reports,[1-4] the present study was done.

Materials and Methods

The gross morphologic and histologic features of the lungs of 35 patients who died while on assisted ventilation or on high concentrations of oxygen were studied at autopsy. For comparison, the morphologic findings from 40 examples of organizing pneumonia, 30 examples of pulmonary edema of various types and causes, and 30 examples of pneumonias of various etiologies were reviewed. Histologic sections from each lobe of both lungs of each patient in all the groups were reviewed independently and without any knowledge of clinical data.

The clinical records of the 35 patients who received assisted ventilation or high concentrations of oxygen were then reviewed to ascertain the major disease states, reasons for and duration of administration of oxygen and assisted ventilation, arterial oxygen tensions achieved, results of tests of pulmonary function, and therapeutic measures utilized.

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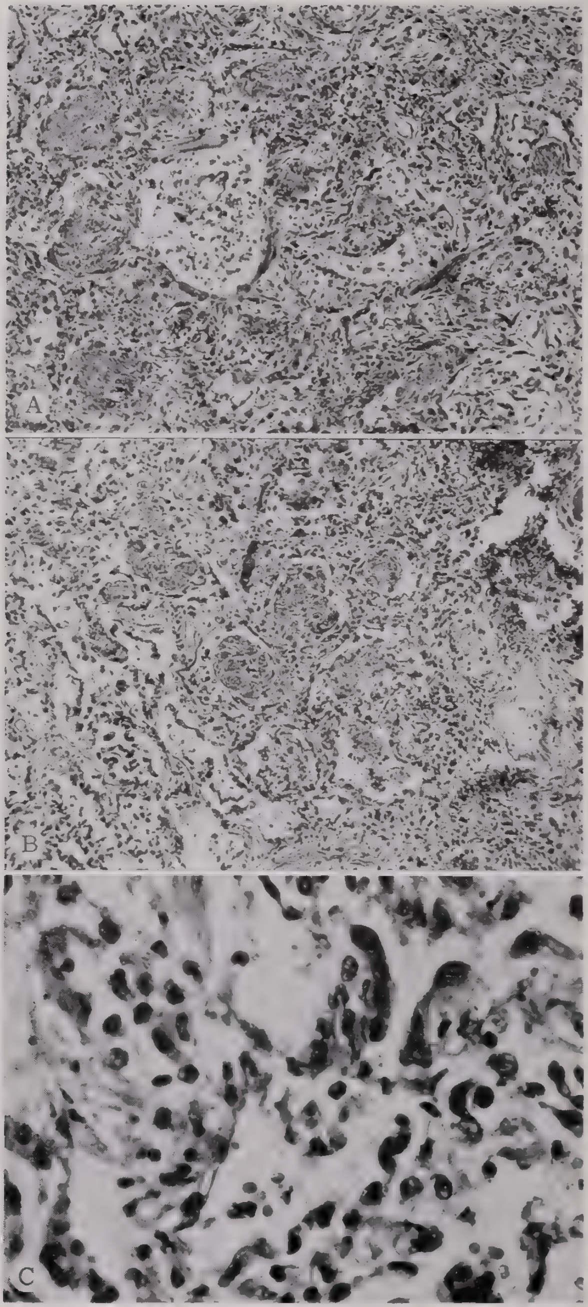

Fig. 1—Morphologic pulmonary lesions. (A) Intra-alveolar deposits of fibrin, hyaline membranes, prominence of alveolar lining cells, intra-alveolar septal thickening with fibroblastic proliferation, and infiltration of chronic inflammatory cells are present. (Hematoxylin and eosin; reduced from x105.) (B) Alveolar septal thickening is more apparent in this area from same case as Figure 1(A). (Hematoxylin and eosin; reduced from x105.) (C) Higher power view of lesion in another case demonstrates prominence of alveolar lining cells (upper right) and nature of inflammatory cells. (Hematoxylin and eosin; reduced from x520.)

Morphologic Features

Weight

Grossly, the lungs of 20 patients with the histopathologic findings tended to be heavy, congested, and firm. The other 15 of the 35 cases did not have these morphologic features. The lung weights in these 20 adults varied greatly, from 655 to 2,860 gm with a mean of 1,580 gm. The mean lung weight of the 100 examples of pneumonias and pulmonary edema was 1,235 gm.

Histologic Changes

The characteristic histologic picture in seven of the 35 cases consisted of intra-alveolar deposits of fibrin, hyaline membranes, thickened alveolar septa with fibroblastic proliferation, prominence of alveolar lining cells, and infiltrates of chronic inflammatory cells (Figure 1A B, C). These 20 cases could be distinguished from pulmonary edema, organizing pneumonia, and the usual varieties of pneumonias by the histologic findings alone.

Clinical Features

The following clinical aspects pertain to the 20 patients in whom the aforementioned morphologic features were present. The 12 males and eight females ranged in age from 15 to 71 years with a mean age of 46 years.

The primary diagnosis is disclosed in Table 1.

Clinically, the respiratory diagnoses were bronchopneumonia in 10 patients, respiratory failure in seven, and aspiration pneumonitis in three.

TABLE I.
Primary Diagnosis (20 Patients)

Traumatic cerebral contusion	5
Metastatic malignancy	5
Primary pulmonary disease (emphysema and chronic asthmatic bronchitis)	2
Respiratory failure (Guillain-Barré syndrome)	2
Systemic lupus erythematosus, tetanus, hepatic coma, coronary heart diseases, postoperative conditions	6

Congestive heart failure was diagnosed in 12 of 20 patients as a terminal event. Seven of the 20 had received vasopressor drugs to sustain blood pressure during their terminal illness. Twelve had received corticosteroid preparations; these were given to five patients for cerebral edema, to three for aspiration pneumonia, to two with hepatic coma, to one patient with asthmatic bronchitis, and to one who had tetanus with evidence of adrenal insufficiency.

Ventilation was carried out through a tracheostomy in 18 of the 20 patients and through an endotracheal tube in the other two.

Laboratory Studies

X-ray Findings

Roentgenograms of the thorax showed evidence of abnormalities in 18 of the 20 patients; 16 had bilateral pulmonary infiltrates (Figure 2) suggestive of pneumonitis with varying degrees of atelectasis and pulmonary vascular congestion, and the other two showed evidence of pleural effusions.

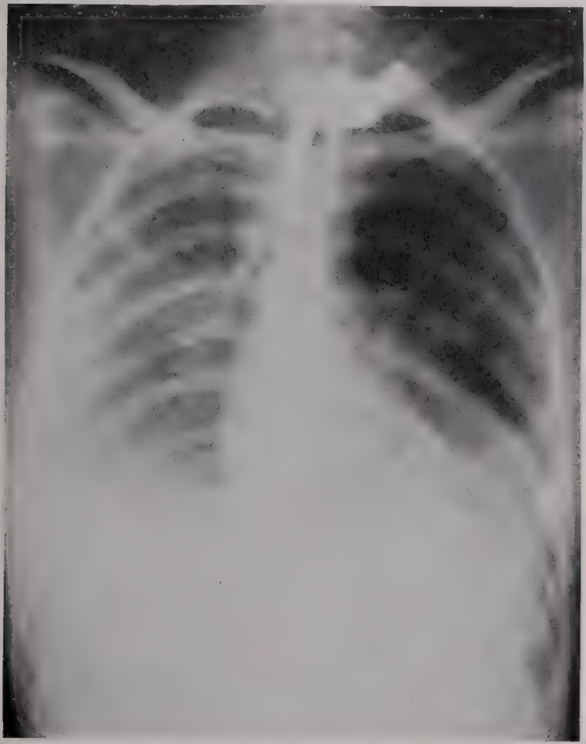

Fig. 2—Example of x-ray pattern of bilateral pulmonary infiltration found in many patients.

Bacteriology

Pathogenic bacterial organisms were cultured from the tracheas of eight of the 20 patients. The organisms obtained were *Pseudomonas* from three, *Diplococcus pneumoniae* from two, *Mima polymorpha* from one, *Bacterium anitratum* from one, and *Alcaligenes faecalis* from one.

Arterial Oxygen

Arterial oxygen levels were measured in 18 patients during the acute phase of the terminal illness; 14 were ventilated with a machine set to deliver 40% oxygen; but the inspired concentration of oxygen probably approximated 60 to 80% since all of these ventilators had humidifiers and nebulizers fed by 100% oxygen. In these 14 patients the observed arterial oxygen tension (Pa_{O_2}) was less than might have been anticipated even if the gas received had contained only 40% oxygen (Table 2). The arterial oxygen tensions in the other four patients who were ventilated with 100% oxygen were also far below the expected normal value for that inspired concentration (Table 3).

TABLE 2.

Arterial Oxygen Tensions in Patients to Whom "40% Oxygen" Was Being Administered Prior to Death

Case	Arterial oxygen tension (Pa_{O_2}),* mm Hg	Days of therapy
1	175	13
2	59	22
3	73	15
4	57	120
5	46	17
6	61	37
7	64	3
8	45	13
9	81	19
10	86	5
11	55	9
12	103	11
13	103	9
14	71	11

*Pa_{O_2} should be approximately 250 mm Hg when fraction of inspired oxygen (FI_{O_2}) = 0.4.

TABLE 3.

Arterial Oxygen Tensions in Patients to Whom 100% Oxygen Was Being Administered Prior to Death

Case	Arterial oxygen tension (Pa_{O_2}),* mm Hg	Days of therapy
15	55	3
16	161	4
17	192	32
18	255	14

*Pa_{O_2} should be approximately 600 mm Hg when FI_{O_2} = 1.0.

Comment

In the 20 patients who died after mechanical ventilation and who had received oxygen at concentrations of 40% or more, the primary diagnosis did not appear to be etiologically significant in the production of the morphologic pulmonary abnormalities. Only one patient had had previous cardiopulmonary disease—a 71-year-old man with emphysema. The respiratory diagnoses of aspiration pneumonia in three patients and bronchopneumonia in 10 probably were not of etiologic significance since 30 patients with various types of pneumonia did not show similar morphologic features. Likewise, pulmonary edema, noted clinically in 12 of the 20 patients as a terminal event, did not seem to be of etiologic significance in the genesis of the pulmonary lesion, because 40 other patients having pulmonary edema did not have the morphologic changes present in the study group.

Drug therapy, including steroids in 12 patients, could not be related to the occurrence of the pulmonary lesion. The difference in histologic features between the 20 patients and the group with pneumonia made infection an unlikely factor in the pathogenesis of the condition. The gram-negative organisms found in six patients most likely reflected contamination introduced through their tracheostomies or from inhalation therapy equipment.

In 19 of the 20 patients, the period of mechanical ventilation ranged from three to 120 days. Although one patient was not ventilated, the same morphologic changes developed after four days of breathing from a mask which delivered 100% oxygen. The only common etiologic factor that could be identified in all patients was the administration of oxygen at high tensions or mechanical ventilation for three or more days.

Morphologically, the commonest gross appearance was one of heavy, firm lungs as described previously by Nash and associates.[1] The mean lung weights of the 20 patients were greater than those of the patients who had other pulmonary abnormalities and who also had greater than normal lung weights. Occasionally, however, the lung weights may be nearly normal in patients who have typical histologic features, as exemplified by one case in the present study in which the total weight of the lungs was 655 gm. The unusual histologic appearance of intra-alveolar deposits of fibrin, hyaline membranes, thickened interalveolar septa, enlarged alveolar lining cells, and chronic inflammatory cellular infiltrate was found to be a distinctive pattern that differentiated patients who had oxygen therapy and assisted ventilation from the control group who had pulmonary edema, organizing pneumonia, and bronchopneumonia owing to various causes.

Conclusion

Histologically, intra-alveolar deposits of fibrin, hyaline membranes, thickened alveolar septa with fibroblastic proliferation, prominence of alveolar lining cells, and infiltrates of chronic inflammatory cells were apparent and seemed specific for the condition.

Histologic changes were present in 20 of the 35 cases. These 20 could be distinguished from pulmonary edema, organizing pneumonia, and the usual varieties of pneumonia by the histologic findings alone. Nineteen of the 20 patients had had assisted ventilation for three to 120 days. The 20th patient had breathed for four days from a mask which delivered 100% oxygen but had not received assisted ventilation. All 20 patients had low partial pressure of oxygen in the arterial blood.

We have concluded that gross and histologic abnormalities occur in the lungs of patients who have been exposed to prolonged mechanical ventilation and to high oxygen concentration. The etiology of these changes may be related to high oxygen tension or inactivation of surfactant,* but we have no evidence from this small retrospective study what the exact mechanism is.

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*See Test Your Word Score Page 1761.

References may be secured from the author or the reprints.

Make good or make room.—Forbes Epigrams

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Non-nursing mothers may begin Ovulen-21 immediately after delivery, on the day of departure from the hospital or at the first postpartum visit, as desired. It is recommended that nursing mothers begin Ovulen-21 four weeks after delivery.

A small fraction of the hormonal agents in oral contraceptive pills has been identified in the milk of mothers receiving these drugs. The long-range effect on the nursing infant cannot be determined at this time.

Indication—Oral contraception.

Contraindications—Thrombophlebitis, thromboembolic disorders, cerebral apoplexy or a past history of these conditions, markedly impaired liver function, known or suspected carcinoma of the breast, known or suspected estrogen-dependent neoplasia, undiagnosed abnormal genital bleeding.

Warnings—Watch for the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, retinal thrombosis); if present or suspected discontinue the drug immediately.

British studies reported in April 1968[1,2] estimate there is a seven- to tenfold increase in mortality and morbidity due to thromboembolic diseases in women taking oral contraceptives. In these controlled retrospective studies, involving 36 reported deaths and 58 hospitalizations due to "idiopathic" thromboembolism, statistical evaluation indicated that the differences observed between users and non-users were highly significant. The conclusions reached in the studies are summarized in the table below:

Comparison of Mortality and Hospitalization Rates Due to Thromboembolic Disease in Users and Non-Users of Oral Contraceptives in Britain.

Category	Mortality Rates		Hospitalization Rates (Morbidity)
	Age 20-34	Age 35-44	Age 20-44
Users of Oral Contraceptives	1.5/100,000	3.9/100,000	47/100,000
Non-Users	0.2/100,000	0.5/100,000	5/100,000

No comparable studies are yet available in the United States. The British data, especially as they indicate the magnitude of the increased risk to the individual patient, cannot be applied directly to women in other countries in which the incidences of spontaneously occurring thromboembolic disease may differ.

Discontinue medication pending examination if there is sudden partial or complete loss of vision, or sudden onset of proptosis, diplopia or migraine. Withdraw medication if papilledema or retinal vascular lesions are found.

Since the safety of Ovulen in pregnancy has not been demonstrated, it is recommended that pregnancy be ruled out for any patient who has missed two consecutive periods before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule the possibility of pregnancy should be considered at the first missed period.

A small fraction of the hormone agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect on the nursing infant cannot be determined at this time.

Precautions—Pretreatment physical examination should include special reference to the breasts and pelvic organs, and a Papanicolaou smear.

Endocrine and possibly liver function tests may be affected by Ovulen. Therefore, it is recommended that such tests if abnormal be repeated after the drug has been withdrawn for two months.

Pre-existing uterine fibromyomas may increase in size under the influence of progestogen-estrogen preparations.

Because these agents may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.

In breakthrough bleeding, and all irregular vaginal bleeding, consider nonfunctional causes. Adequate diagnostic measures are indicated in undiagnosed vaginal bleeding.

Carefully observe patients with a history of psychic depression and discontinue the drug if severe depression recurs.

Any possible influence of prolonged Ovulen therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study.

A decrease in glucose tolerance has occurred in a significant percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be observed carefully while receiving Ovulen.

Because of the effects of estrogens on epiphyseal closure Ovulen should be used judiciously in young patients in whom bone growth is not complete.

The age of the patient constitutes no absolute limiting factor, although Ovulen therapy may mask the onset of the climacteric.

The pathologist should be informed of Ovulen therapy when relevant specimens are submitted.

Adverse Reactions—A statistically significant association has been shown between use of oral contraceptives and the following serious adverse reactions: thrombophlebitis, pulmonary embolism.

Although available evidence is suggestive of an association, such a relationship has been neither confirmed nor refuted for the following serious adverse reactions: cerebrovascular accidents, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions are known to occur in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea during and after treatment, edema, chloasma or melasma, breast changes (tenderness, enlargement, secretion), change in weight, changes in cervical erosion and cervical secretions, suppression of lactation when given immediately post partum, cholestatic jaundice, migraine, allergic rash, rise in blood pressure in susceptible individuals, mental depression.

Although the following adverse reactions have been reported in users of oral contraceptives, an association has been neither confirmed nor refuted: anovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme and nodosum, hemorrhagic eruption, itching. The following laboratory results may be altered by oral contraceptives: hepatic function: increased sulfobromophthalein and other tests; coagulation tests: increase in prothrombin, Factors VII, VIII, IX and X; thyroid function: increase in PBI and butanol extractable protein bound iodine, and decrease in T^3 uptake values; metyrapone test; pregnanediol determination.

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References: 1. Inman, W. H. W., and Vessey, M. P.: Brit. Med. J. 2:193-199 (April 27) 1968. 2. Vessey, M. P., and Doll, R.: Brit. Med. J. 2:199-205 (April 27) 1968.

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Editorials

Pernicious Anemia

PERNICIOUS ANEMIA is one of the diseases that make the practice of medicine rewarding. The patient, often seriously ill, is restored to complete health by simple measures. The response is predictable. The physician has a feeling of self satisfaction not only at making the diagnosis but in so readily curing an illness formerly fatal.

The story of pernicious anemia is one of the triumphs of modern medicine, with the discovery of the therapeutic effect of liver by Minot and Murphy, the experiments of Castle on the anti-pernicious anemia principle, and the isolation and synthesis of vitamin B12. Glass' two hundred and seventy-three page article on the intrinsic factor with its 1311 references clearly attests to the continued interest in this field.[1]

The February issue of Minnesota Medicine* contains an article on the occurrence of pernicious anemia in two American Indians. The authors point out the rarity of this anemia in individuals of presumed Oriental origin, including Eskimos and North American Indians. In both cases the disease had primarily neurological manifestations with only moderate anemia. Whether or not such a pattern is generally true in individuals of this descent is not evident from the literature. Administration of folic acid will produce hematological remission but apparently provokes the onset of subacute combined degeneration. Duration of illness prior to therapy is important; otherwise we do not know why some individuals are more prone to the neurological manifestations. Difference in racial susceptibility might well offer a clue.

Current interest centers around the question of whether pernicious anemia is an auto-immune disease. A high incidence of antibodies against thyroid, parietal cells of the stomach, and intrinsic factor has been found in patients with pernicious anemia. It has been proposed that the fundamental defect in this disease is the production of antibodies which bind intrinsic factor, subsequently preventing the absorption of vitamin B12. The frequent occurrence of the antibodies has been clearly demonstrated. Whether or not they are of significance is uncertain, for they are not always found. Pernicious anemia occurs in immunologically deficient people, etc.[2,3]

The precise biochemical action of vitamin B12 is under investigation. Megaloblastic anemia is believed to represent a partial failure of DNA synthesis relative to that of cytoplasmic RNA; hence the maturation arrest of the nucleus with a "young" nucleus and "old" cytoplasm. Coenzyme B12 appears to be involved in multiple metabolic systems; it is required in the succinic† acid cycle, the synthesis of proteins, the function of sulfhydryl-activated enzyme systems, the synthesis of deoxyriboside, etc.[4] It is also essential for "normal growth and nutrition, normal hematopoesis, normal

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*Olin, Ronald, and Harrington, Ryan B.: Pernicious Anemia in North American Indians. Minnesota Med 52:243, 1969.

†See Test Your Word Score Page 1761.

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production of all epithelial cells, and for maintenance of myelin throughout the nervous system."[5]

There is no evidence that vitamin B12 has any therapeutic effect except in pernicious anemia and subacute combined degeneration. It is a travesty that it is mainly used as a placebo. It does not affect other forms of neuritis and it certainly is not a cure for "fatigue."

Paul T. Lowry, M.D.
Minneapolis, Minnesota

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1. Glass, G. B. G.: Gastric Intrinsic Factor and Its Function in the Metabolism of Vitamin B12. Physiol Rev 43:529, 1963.
2. Herbert, V. and Castle, W. B.: Medical Progress Intrinsic Factor. New Eng J Med, 270:1181, 1964.
3. Bardhan, K. K., Hall, J. R., Spray, G. H. & Callender, S. T. E.: Blocking and Binding Autoantibody to Intrinsic Factor. Lancet 1:62, 1968.
4. Beck, W. S.: The Metabolic Basis of Megaloblastic Erythropoiese. Medicine 43:715, 1964.
5. Herbert, V.: Drugs Effective in Megaloblastic Anemias: Vitamin B12 & Folic Acid, Chapter 64 in Pharmacological Basis of Therapeutics, Goodman & Gilman (eds.) New York: The MacMillan Co., 1965.

Three Problems—One Solution

THE NEEDS OF THE community, or the individual, frequently come at inopportune times and require inefficient, inconvenient, and expensive solutions. Thus, when we observe several community needs and the opportunity to serve all with one stroke, we gain convenience, efficiency, and economy. This plan, which could simultaneously resolve a current problem (what to do with Gillette Hospital) and advance the solution of two other problems (increasing the number of physicians in Minnesota and improving the care of children crippled by chronic disease), deserves debate.

Problem one—Gillette State Hospital for Crippled Children was studied by a Subcommittee of the Minnesota Senate Public Welfare Committee. The last paragraph of the Committee's report stated:

> "In the final analysis, the question of continuing Gillette revolves around considerations of the total program of care and treatment supported by the State for handicapped children, the extent to which existing programs at Gillette can be continued at a reasonable cost, and the extent to which new facilities can be provided which are flexible enough to be changed as needed in keeping with changing trends and needs for patient care."

Problem two—increasing the number of physicians in Minnesota. Recommendations have been made to increase the number of medical students at the University Medical School from 150 to 200 and to develop graduate basic science programs at the University of Minnesota, Duluth, with eventual use of this base to form a four-year medical school. Increased funds for construction of additional beds will be required to provide care for the patients needed to train these additional doctors.

Problem three—children crippled by chronic disease. At one time the term "crippled child" meant the child who was handicapped by a skeletal or neuromotor disease. The problems encompassed by this old concept have changed radically in the past twenty years. Three of these diseases, poliomyelitis, osteomyelitis and tuberculosis, which once caused one half of Gillette Hospital admissions, have almost vanished. The remaining crippling problems are proving more complex; to accomplish rehabilitation the orthopedic surgeon requires other medical specialists to aid in the care of afflicted patients. This evolution of understanding that social, psychiatric, sensory, and learning problems can be additional handicaps to the orthopedically crippled child has been accompanied by a recognition that children handicapped by other chronic diseases can also be crippled in their ability to achieve their optimum potential in their pursuit of self-expression and development.

Today the Crippled Children Services of the United States Government recognizes that a crippled child is one who "has an organic dis-

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UNDER LICENSE FROM BOEHRINGER INGELHEIM G.M.B.H. GEIGY PHARMACEUTICALS, DIVISION OF GEIGY CHEMICAL CORPORATION, ARDSLEY, NEW YORK 10502 ease, defect or condition which may hinder the achievement of normal growth and development."

The broadened scope of this definition extends support for the care of children beyond the traditional limits of orthopedic conditions. In Minnesota such other diseases include surgically treatable defects of the skin, both congenital and acquired, including burns; heart lesions amenable to surgery; dental handicapping conditions; hearing defects; cystic fibrosis; mentally retarded patients with treatable physical handicaps, plus other handicapping conditions amenable to treatment, whether gastrointestinal, genital-urinary, pulmonary neurologic or inherited.

Some children with some of these crippling diseases fail to obtain their maximum potential because they have no access to physical facilities for specialized long-term care such as exist for orthopedic problems in Gillette State Hospital and the Shriner's Hospital for Crippled Children. Optimum care cannot be provided for many of these children until rehabilitation facilities are created which can provide such long-term care for patients with any of these problems.

Solution—Build a new Gillette State Hospital for handicapped children as a 350-to-450-bed children's hospital into the hospital complex at the University of Minnesota Medical School or as a smaller children's hospital in Duluth, to be the first building of the University of Minnesota—Duluth Medical School.

Such a decision would permit maintenance of a historic hospital and would establish a needed and now non-existent facility that could provide total comprehensive and consultative care for children with all varieties of acute and chronically-handicapping disorders. In either location such a new Gillette State Hospital for Handicapped Children would simultaneously resolve some of the problems in the cost of developing more doctors and some of the problems of chronically handicapping childhood diseases. Any other solution would require two or three comparably expensive decisions to approximate the effects of this one. If Gillette State Hospital for Crippled Children is rebuilt as a narrowly directed Children's Orthopedic Hospital, additional facilities will still be needed to provide care for the other chronic childhood disease problems; otherwise we will continue to provide less than adequate care for some of these children and eventually incur increased expenses through support programs for disabled adults.

Rebuilding Gillette Hospital as a hospital for chronic children's diseases as a State Children's Hospital at the University of Minnesota or as the first building of the University of Minnesota—Duluth Medical School would conveniently and economically resolve the problem of what to do about Gillette Hospital, speed the training of additional physicians in Minnesota and provide a needed facility for care of children with many non-orthopedic crippling diseases.

Warren J. Warwick, M.D.*
Minneapolis, Minnesota

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*Associate Professor, Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota.

The Human Use of Human Machines

THE TROUBLE with doctors as scientists is that they tend to act like humans. Take, for example, the act of listening to a heart. Every listener responds differently to the same sounds. Indeed, the same observer on different occasions may interpret the same sound differently, depending on his inner ear, his mood, and his prejudices. Which should come as no surprise since cochlea, like minds, aren't always cocked at the same angle.

Auscultation, then, is a subjective act, subject to human frailties. To use computer talk, the mind's ear supplies only "soft data." But, no matter; as every modern schoolboy knows, machines can harden the softest figures.

They can do something else, too. As Doctor Wanamaker points out in a previous issue of *Minnesota Medicine,** a machine (in this case a phonocardiogram) can teach. By providing a graphic record, the phonocardio-

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*Wanamaker, J. L.: Value of Graphic Methods. Minnesota Med 52:549, 1969.

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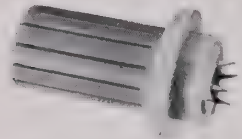

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gram lets the physician "see" what he heard, tells him something of a lesion's severity, and provides a record for future scrutiny. And, to quote Doctor Wanamaker, it ". . . can teach the important lesson of humility and serve as a valuable supplemental method of study."

But before you leap to the conclusion that the machine will take the guess-work out of listening, consider another piece of work. With a machine (this time a phonocardioscan), investigators at the Permanente Medical Group in California auscultated the hearts of 456 adults and then compared the results with those obtained by internists.[1] The machine didn't fare too well. Of the murmurs it detected, a third turned out to be insignificant. And when murmurs were present, it missed a fourth of them.

The conclusion? "At its present stage of development, the machine was considered insufficiently sensitive and specific for incorporation into a multiphasic health appraisal examination of adults." Take heart. Maybe machines are human after all.

Richard L. Reece, M.D.
Minneapolis, Minnesota

Reference

1. Klatsky, A. L., Bolomey, A. A., and Siegelaub, A. B.: Auscultation of the Adult Heart by Machine. New Engl J Med 279:230, 1968.

Chronic Respiratory Disease in Children

Dr. Edwin Kendig* states in his review: "Chronic respiratory disease in children has been considered unglamorous." However, the content of the articles on this subject in the September issue of MINNESOTA MEDICINE indicates that much progress is being made in this field, both diagnostically and therapeutically. In pulmonary function studies the exceedingly complex metabolic function of the lung is being appreciated, as pointed out by Dr. V. Chernick,* and sophisticated radioisotope studies have been described by Dr. Jose R. Medina* in localizing pulmonary functional lesions. Newer concepts regarding the pathogenesis of cystic fibrosis are presented by Drs. Alexander Spock* and Gordon E. Gibbs,* and Dr. Malcolm N. Blumenthal* has reviewed very clearly the current knowledge and controversies regarding the etiology of bronchial asthma. Dr. Norman Hepper* presents current data on the effects of cigarette smoking in the production of chronic respiratory disease and Dr. LeRoy W. Matthews* has explained the role of inhalation therapy in its management. Dr. Richard Hong's* excellent conceptualization of the physiology of immunity is especially worthy of review.

For the "front line" physician, seeing children in health and disease, a most important contribution is the article by Dr. William Waring* on the clinical evaluation of the child with chronic lung disease. Clinical awareness of chronic respiratory disease which often begins insidiously in childhood may be greatly enhanced by the routine use of the rather simple quantitative techniques described by Dr. Waring. Accurate counting of the respiratory rate (which may best be done by enlisting the help of parents during the child's sleep), measurements of thoracic depth and width with obstetrical calipers and a simple clinical evaluation for clubbing of the fingers provide easily obtainable data. These measurements provide a base line for suspicion of developing disease and a way to follow its progress. The advantage of this kind of measurement is that it is not effort-dependent on the part of the child. Anyone who has worked extensively with pulmonary function testing in children realizes the need for simple diagnostic tools for case finding. Cough, as a pediatric symptom, is so ubiquitous that it may be easily disregarded, but chronic cough (daily for three months or more) must be taken seriously, as Drs. Waring and Harris* point out.

Bronchial asthma, as an example of the most common of chronic respiratory diseases in children, is a major interest of the pediatric aller-

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*See September issue, Minnesota Med 52:1363, 1373, 1407, 1429, 1433, 1435, 1445, 1455, 1465, and 1483.

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References: 1. Jaffe, J. H.: in Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, 3rd ed., 1965, pp. 279-280. 2. Woods, L. A., in Drill, V. A.: Pharmacology in Medicine, 1958, pp. 226-227. 3. Goth, A.: Medical Pharmacology, 2nd ed., 1964, pp. 336-337. 4. Beckman, H.: Pharmacology, 2nd ed., 1961, pp. 180-183. 5. LaBrecque, D. C.: Curr. Ther. Res. *8*: 106-109, 1966. 6. Dunlop, E.: J. Amer. Geriat. Soc. *16*:343-349, 1968.

gist. Besides its prevalence an important facet of bronchial asthma in childhood is its reversibility. While the long-term natural history of bronchial asthma is poorly understood. Rackemann's study* indicated that 70 per cent of children with asthma are virtually symptom-free by age 20.

However, any physician who cares for children with asthma realizes what a disabling disease it can be, both physically and psychologically. As a major cause of school absence among chronic diseases, childhood bronchial asthma also is a community problem. Overprotection and sheltering of the child with asthma, often fostered by physicians' rigid and authoritarian instructions to well-meaning parents, have made the child with asthma fearful, inhibited and of low self-concept. At the other end of the spectrum, casual treatment of bronchial asthma in the child, while waiting for "tincture of time" to solve the problem, can lead to much unnecessary suffering, self-depreciation and disability.

What is needed is a vigorous, reasonable multi-disciplined approach to the problem of the child with bronchial asthma which leads to the acceptance of his limitations by the child, his family, and the community. These limitations should be determined, not by fear and admonition, but by experience with, and observations of, the individual child. Parents, physicians, vocational counselors, school nurses, educators, physical education directors and all others involved in the health supervision of children, must be made aware of these concepts.

Programs to improve the quality of life for children with asthma, such as the physical conditioning and parent education courses sponsored by the Respiratory Disease Associations of both Hennepin and Ramsey Counties, the Asthma Camp, similarly supported, and the adaptive physical education programs in some of the public school systems are important approaches in action now. Expansion of services such as these to other areas of the state deserve our active support.

Richard T. Cushing, M.D.
Minneapolis, Minnesota

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*Rackemann, F. M. and Edwards, M. C.: Asthma in Children. A Follow-up Study of 688 Patients after an Interval of Twenty Years. New Eng J Med 246:815, 858, 1952.

Test Your Word Score

Surfactant—*a surface-active agent* (page 1748).

Succinic—*pertaining to a colorless crystalline diacid* (page 1753).

Athetoid—*characterized by slow vermicular movements of the hands and feet, occurring in constant succession* (page 1779).

Lichen planus—*an inflammatory skin disease with wide, flat papules, often persistent and occurring in circumscribed areas* (page 1804).

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Trocar—from French *trois quarts* (three quarters)

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Your manuscript is both good and original; but the part that is good is not original, and the part that is original is not good.—Samuel Johnson

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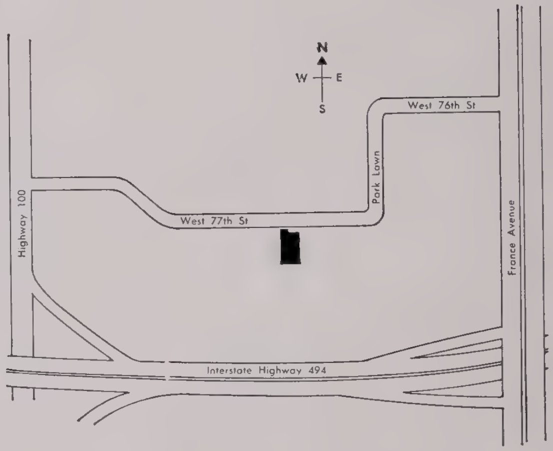
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You May Be Right

The legitimate purpose of a journal is educational and the legitimate concern of our state journal's editor is the quality of education in Minnesota. I was, therefore, pleased to see Dr. Rice asking hard questions about a particular educational program in Minnesota sponsored by the Regional Medical Programs. The Regional Medical Programs were conceived by our Federal Government to meet pressing needs to educate doctors far removed from medical centers in the latest management practices for certain diseases—particularly cancer, heart disease and stroke. Thousands of patient lives would be saved, it was felt, if only the out-lying physicians could be taught how to manage their patients "properly." An elaborate well-funded program was established in many regions across America in response to this need and our State established the Northlands Regional Medical Program. Enthusiasm ran high and many factions in the State of Minnesota became involved. An organization was set up and staff was hired. All this took place some years ago.

Now concerned physicians must ask, "What has been done by the Northlands Medical Region Program? What is being done currently and what plans are being laid for the future? Are physicians in the peripheral areas of Minnesota being served regarding their educational needs or has the government merely created still another bureaucratic self-serving institution which does not meet the needs of doctors and their patients? Have valuable tax dollars been invested wisely in medical and paramedical educational programs in our State or are existing facilities being duplicated?"

Dr. Carl Rice has focused attention on one of the activities of the Northlands Regional Medical Program—namely, the canned consultation whereby physicians may call a number and receive a transcribed message regarding a medical problem. He pointed out that consultants in the State abound and a phone call to any would surely bring about a response and the referring physician would at least have a chance to interact with the respondent. Traditionally, medicine has been practiced by fostering warm interchanges among colleagues. The tax dollars spent on developing the canned program might better have been invested in medical and paramedical personnel, on defraying expenses of trained medical teachers invited to peripheral hospitals to talk and interact with their colleagues. The questions raised in Dr. Rice's insightful soliloquy are most serious and should foment doubts in the minds of all concerned physicians about the value of the Northlands Regional Medical Program. Perhaps it is time that our State Medical Journal lend its influential voice to an inquiry as to what our Regional Medical Program is doing. Perhaps it is time for concerned readers of Minnesota Medicine to have answers regarding the expenditure of funds ostensibly for their benefit.

Milton Alter, M.D., Ph.D.*
Minneapolis, Minnesota

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*Associate Professor, Director, Epidemiology and Genetics Unit, Department of Neurology, Veterans Hospital.

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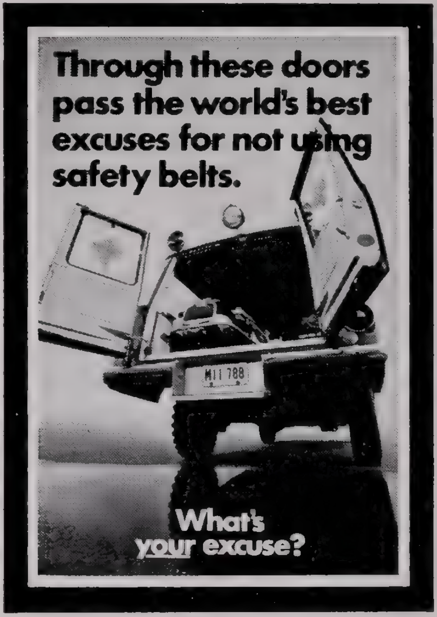

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You May Be Right

(Continued)

You May Be Right, but . . . had I edited the October issue of MINNESOTA MEDICINE, I would have reversed, on page 1639, the position of the Editor's Soliloquy, and the immediately following quotation from Old Doc Hess.

I like an apertif to sharpen my perceptions, and alert my comparative conclusions.

R. P. Buckley, M.D.
Duluth, Minnesota

You May Be Right but . . . Your comments with regard to "Canned Consultation"* were of interest and I might add that one and a quarter million dollars is sufficient to provide a comfortable income for 40 fulltime physicians or, in lieu of that, the care of the doctor bills for 4,000 families through the Medallion plan of the Minnesota Blue Shield. L.G.

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*Minnesota Medicine 52:1639, 1969.

I read with interest the article entitled "Infarct of the Prostate Causing Pyohydronephrosis" by Stanley J. Antolak, Jr., M.D., in the April 1969* issue of MINNESOTA MEDICINE. I think Dr. Antolak is to be congratulated on his carefully planned and essentially conservative and successful therapy of this difficult problem.

However, I do not agree with the interpretation placed on the finding of the infarct of the prostate. I think a much more likely cause for the anuria and distal ureteral obstruction is impaction of cellular or calculous debris from the already infected kidney. The temporary obstruction at the left ureteral orifice relented sometime after the performance of the nephrostomy and again urine passed freely into the bladder.

I feel that there is no reason to suspect that the infarct is other than an incidental finding noted only because the patient subsequently underwent transurethral resection of the prostate gland. I can think of no physiopathologic process that would allow infarction in the left posterior apical segment of the prostate to cause distal ureteral obstruction. The 43-year history of urinary calculi is reason enough for the phenomenon noted.

J. M. Streitz, M.D.
Duluth, Minnesota

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*Page 591.

The Doctor

Medicine, the only profession that labors incessantly to destroy the reason for its own existence.—James Bryce

A conservative is a man who just sits and thinks, mostly sits.—Woodrow Wilson

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The Editor's Soliloquy

LEGALLY CORRECT

Years ago when I began the practice of surgery, it was customary to insist that the pathologist find an abnormal cell in a normal appendix for fear of being legally incriminated for the removal of a normal, though useless, organ. Surely there were not many instances in which the surgeon deliberately removed a normal appendix, though in the interest of choosing a less hazardous course in preference to the risk of a greater mortality, a surgeon did occasionally find that the appendix was normal.

Within a few years this trend was reversed on the basis that there was no legal liability when a justifiable error in diagnosis had to be admitted to the anxious parents. Forthright integrity prevailed and no official document was necessary to maintain the legality of the appendectomy.

In recent years it seems that a proportionately large percentage of the budgets of medical societies is being expended for non-scientific ventures. Might it not be wiser to allocate a greater proportion of the budget to our major educational pursuits. With intellectual integrity it would normally follow that there would be fewer libelous things to fear. In that high-grade, honorable medicine can be practiced only by staying abreast of the scientific advances through conscientious study, reading of medical literature, and attendance at scientific meetings, is it possible to stay within the intellectual field of medicine. A few extra dollars for that purpose should not be catastrophic.

Carl O. Rice, M.D.

OLD DOC HESS SAYS: Fear not a legal liability—for if, in the practice of your profession, you are intellectually honest, you will in all probability be legally correct.—C.O.R.

Guest Consultant

At parties he's in much demand:
The hostess seats him close at hand
And all the guests are pleased as Punch
He came to dinner or to lunch.

And is he, then, a beau, a wit,
By whom the ladies like to sit?
Oh, no—each hopes the guest M.D.
Will diagnose her ailments free.*

---

*Richard Armour: The Medical Muse, 1963.

Thinking

I wrote somewhere once that the third-rate mind was only happy when it was thinking with the majority, the second-rate mind was only happy when it was thinking with the minority, and the first-rate mind was only happy when it was thinking.
—A. A. Milne

President's Letter

(Continued from Page 1723)

mittees of physicians to prevent such overutilization. Here again the American Society of Internal Medicine is active in implementing and properly directing the quality and utilization control committees.

Only major problems have been alluded to here. It is apparent, however, that many dedicated physicians are giving a great deal of time to achieving the aims of the American Society of Internal Medicine. Unless more of us are willing to forego our usually passive role and help direct the changes which keep occurring in medicine, we will find ourselves in danger of having our freedom limited because we have not stood up to our responsibilities.

Herbert W. Johnson, M.D.
President
Association of Minnesota Internists

Man Facing Man

All medicine, the magical and mysterious relationship between physician and patient, which contributes so much to the healing process, is founded on knowing how to produce a good clinical case history. I prefer a good clinical case history, based on a naturalistic and psychological criterion, to the best laboratory reports. In turn, the dialogue with the patient, which makes a good clinical case history possible, is in itself incontestably a healing function.

A man is facing another man. They are alone. Even if there were people around them, they would still be alone in the seventh solitude of their mysterious relationship. One of them is ill and in pain. The other knows how to alleviate him.

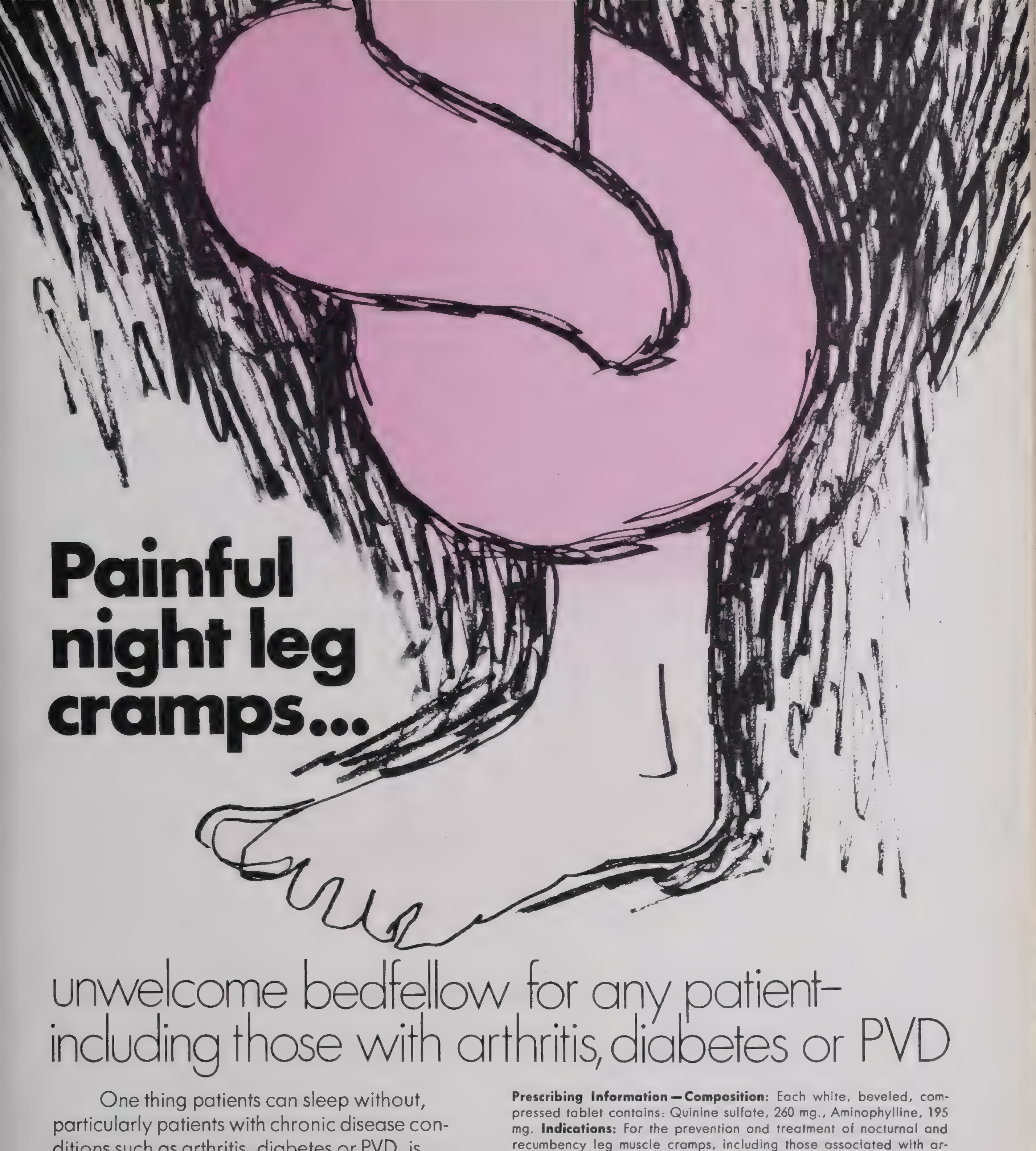
They may be standing by the pyramid at Sakkara five thousand years ago under the blazing Egyptian sun; or in the shade of a palm tree on the island of Cos some twenty-four centuries ago; or at the papal court of Avignon during the Black Death; or in the palace of a sixteenth-century Italian doge; or in the London of James I in the sanctum of a physician who impatiently glances at his timepiece wondering if he will be late for the new Shakespeare play at the Globe Theater; or in Maria Theresa's imperial Vienna, famous for music and medicine; or in the Necker Hospital in Paris in the days when the memory of Napoleon still sent cold shivers down the spines of the monarchs of Europe; or in Boston where for the first time tremendous progress in neurosurgery is being made; or in the New York of modern skyscrapers and electronic marvels.

One of the two men is a patient. The other is a physician, and he may bear the name of Imhotep, Hippocrates, Guy de Chauliac, Fracastoro, William Harvey, Auenbrugger, Laennec, Cushing, or that of a New York physician of our own day.

A simple inspection of that scene between the two men, of the act of diagnosis, which is at the same time prognostic and curative, teaches us something very important. Through the centuries, for some six thousand years now, the patient has not changed. His *history,* his biographical adventure has changed, but his nature has always remained the same. But the physician has changed. His knowledge, his technique, his social standing have all changed, though not his healing mission nor his humanitarian ethics. No, the patient has not changed during all those centuries, but the physician has and with him the world of medicine.*

---

*Felix Marti-Ibanez, M.D.: The Patient's Progress, 1962.



Painful night leg cramps...

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One thing patients can sleep without, particularly patients with chronic disease conditions such as arthritis, diabetes or PVD, is painful night leg cramps. Although seldom the presenting complaint, night leg cramps can tie your patients up in painful knots. Now, just one tablet of QUINAMM at bedtime can usually bring an end to shattered sleep and needless suffering. Your patients will sleep restfully—gratefully—with QUINAMM, specific therapy to prevent painful night leg cramps.

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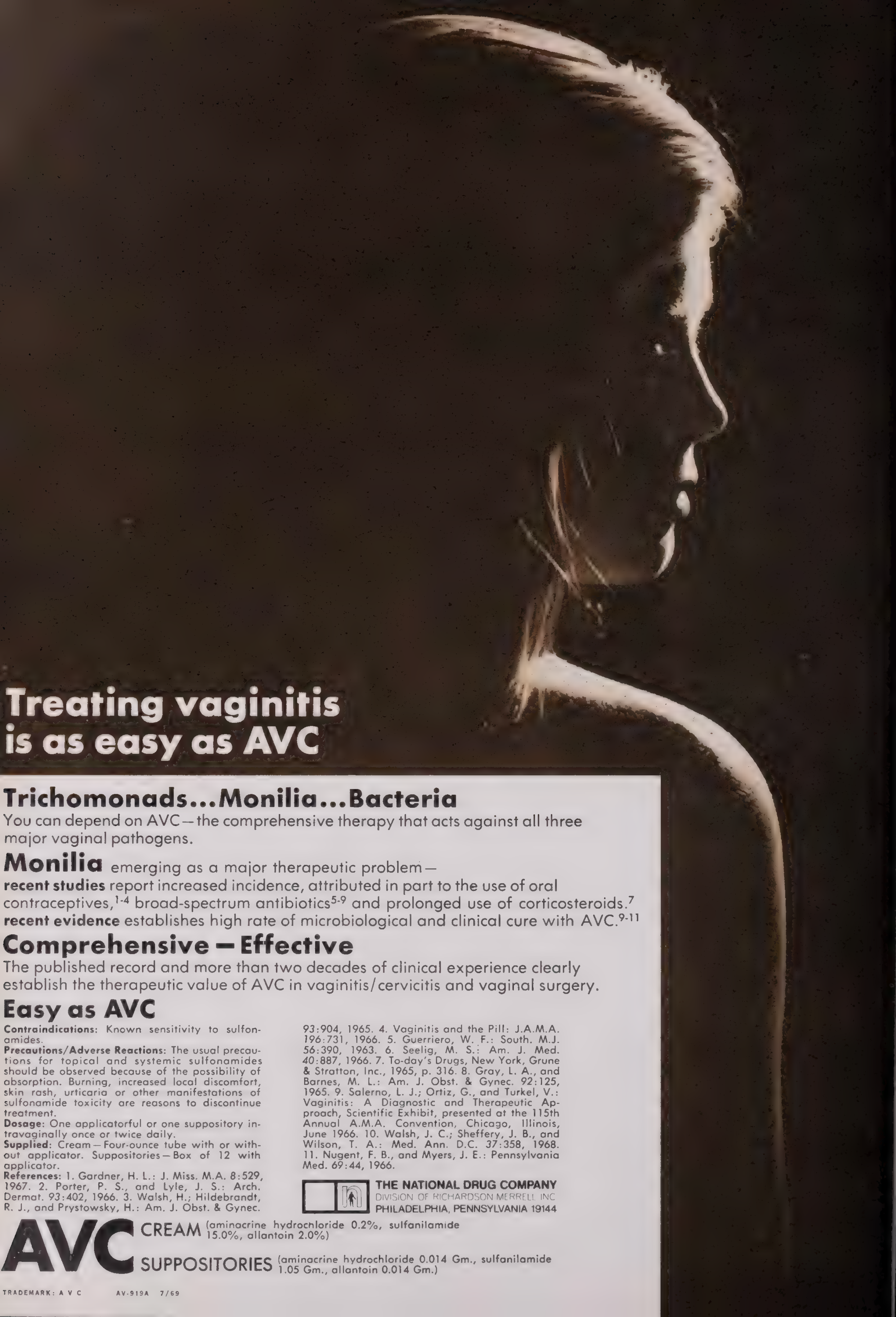

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You can depend on AVC—the comprehensive therapy that acts against all three major vaginal pathogens.

Monilia emerging as a major therapeutic problem—
recent studies report increased incidence, attributed in part to the use of oral contraceptives,[1-4] broad-spectrum antibiotics[5-9] and prolonged use of corticosteroids.[7]
recent evidence establishes high rate of microbiological and clinical cure with AVC.[9-11]

Comprehensive—Effective

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Contraindications: Known sensitivity to sulfonamides.
Precautions/Adverse Reactions: The usual precautions for topical and systemic sulfonamides should be observed because of the possibility of absorption. Burning, increased local discomfort, skin rash, urticaria or other manifestations of sulfonamide toxicity are reasons to discontinue treatment.
Dosage: One applicatorful or one suppository intravaginally once or twice daily.
Supplied: Cream—Four-ounce tube with or without applicator. Suppositories—Box of 12 with applicator.
References: 1. Gardner, H. L.: J. Miss. M.A. 8:529, 1967. 2. Porter, P. S., and Lyle, J. S.: Arch. Dermat. 93:402, 1966. 3. Walsh, H.; Hildebrandt, R. J., and Prystowsky, H.: Am. J. Obst. & Gynec. 93:904, 1965. 4. Vaginitis and the Pill: J.A.M.A. 196:731, 1966. 5. Guerriero, W. F.: South. M.J. 56:390, 1963. 6. Seelig, M. S.: Am. J. Med. 40:887, 1966. 7. To-day's Drugs, New York, Grune & Stratton, Inc., 1965, p. 316. 8. Gray, L. A., and Barnes, M. L.: Am. J. Obst. & Gynec. 92:125, 1965. 9. Salerno, L. J.; Ortiz, G., and Turkel, V.: Vaginitis: A Diagnostic and Therapeutic Approach, Scientific Exhibit, presented at the 115th Annual A.M.A. Convention, Chicago, Illinois, June 1966. 10. Walsh, J. C.; Sheffery, J. B., and Wilson, T. A.: Med. Ann. D.C. 37:358, 1968. 11. Nugent, F. B., and Myers, J. E.: Pennsylvania Med. 69:44, 1966.

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Curbstone Consultation

Reconstructive Surgery

QUESTION: What are the indications for referring patients for reconstructive surgery in arterial occlusive disease of the lower extremities?

ANSWER: A patient should be considered a potential candidate for reconstructive surgery if he has severe calf claudication which incapacitates him in carrying out his work or essential activities, if he experiences severe ischemic rest pain in the involved extremity, or if early gangrenous changes have occurred in the foot or toes. Patients with symptoms referable to one or more of these categories comprise the pool of potential candidates for reconstructive arterial surgery. The final selection of any given patient for surgery, however, must await the outcome of a femoral arteriogram. This diagnostic study is done to determine whether or not an adequate distal runoff exists. Although a single open artery is sufficient to proceed with reconstructive surgery, the chances of achieving success will vary directly with the number of patent branches at the popliteal trifurcation.

Some surgeons feel it is permissible to forego a femoral arteriogram in those instances in which amputation is the alternative to a reconstructive procedure. Under these circumstances the runoff distally can be checked at the time of surgery by an arteriotomy in the popliteal artery and by noting the degree of backflow. If backflow is insufficient to permit reconstructive surgery, then amputation is carried out. It is my personal feeling that femoral arteriography should be secured whenever possible, either at the time of surgery or beforehand, to take advantage of the more quantitative information which it can provide.

Harold D. Kletschka, M.D.
Montgomery, Alabama

Science

In the middle of the nineteenth century a dogged English mathematician named Shanks computed the value of *pi*, the ratio of the circumference of a circle to its diameter, to 707 decimal places. The job took more than fifteen years. Later mathematicians were content to let Shanks hold the record.

Recently, some mathematical machine operators presented the problem to Eniac, the all-electronic calculator. The machine's 18,800 tubes went into action and computed *pi* to 2,040 places. Time: under twenty-four hours.

Meetings and Announcements

Mayo Clinic Clinical Reviews

A program of lectures and discussions on problems of general interest in medicine and surgery will be held at the Mayo Clinic and Mayo Foundation, Rochester, Minnesota. Identical sessions are offered on November 3, 4, 5, 1969 and November 10, 11, 12, 1969.

This program is acceptable for credit by the American Academy of General Practice and the College of Family Physicians of Canada. The registration fee for this program is $20.

The number of physicians who can be accommodated is necessarily limited. For this reason identical programs will be offered two successive weeks. The program will be presented first on November 3, 4, 5, and repeated on November 10, 11, 12. Those wishing to attend should communicate with M. G. Brataas, Mayo Clinic, Rochester, Minnesota 55901, indicating which session they would prefer to attend.

Clinical Neurology Fellowships

Fellowships in Clinical Neurology have been established at the Minneapolis Veterans Administration Hospital.

General Practitioners and Non-Neurological Specialists are invited to apply for an intensive postgraduate training experience on the Neurological Wards at the Minneapolis VA Hospital. Programs are designed to provide one to four weeks of supervised bedside and didactic instruction in the diagnosis and treatment of neurological disease. Those accepted for the fellowship may receive quarters, if desired. Fellows may elect any one or a combination of the following programs:

Week 1—The Neurological Examination
Week 2—Special Neurological Diagnostic Procedures
Week 3—Latest Treatments of Acute and Chronic Neurological Problems
Week 4—Frontiers of Neurological Research

Each program will commence on Monday and terminate on Friday.

Apply to Milton Alter, M.D., Ph.D., Chief, Neurology Service, Veterans Administration Hospital, 54th St. and 48th Ave. So., Minneapolis, Minnesota 55417.

Hennepin County Academy of General Practice

The Hennepin County Academy of General Practice is again sponsoring an invitational banquet on Monday evening, November 17, 1969. The affair will be held at the Radisson Hotel at 6:00 p.m. Speaker will be Mr. Harold P. Pluimen. The title of his presentation is, "The Frontiers of Our Times". Contact Donald L. Wright, M.D., 3620 Central Avenue N.E., Minneapolis, Minnesota, Telephone (612) 781-3494.

American Board of Family Practice

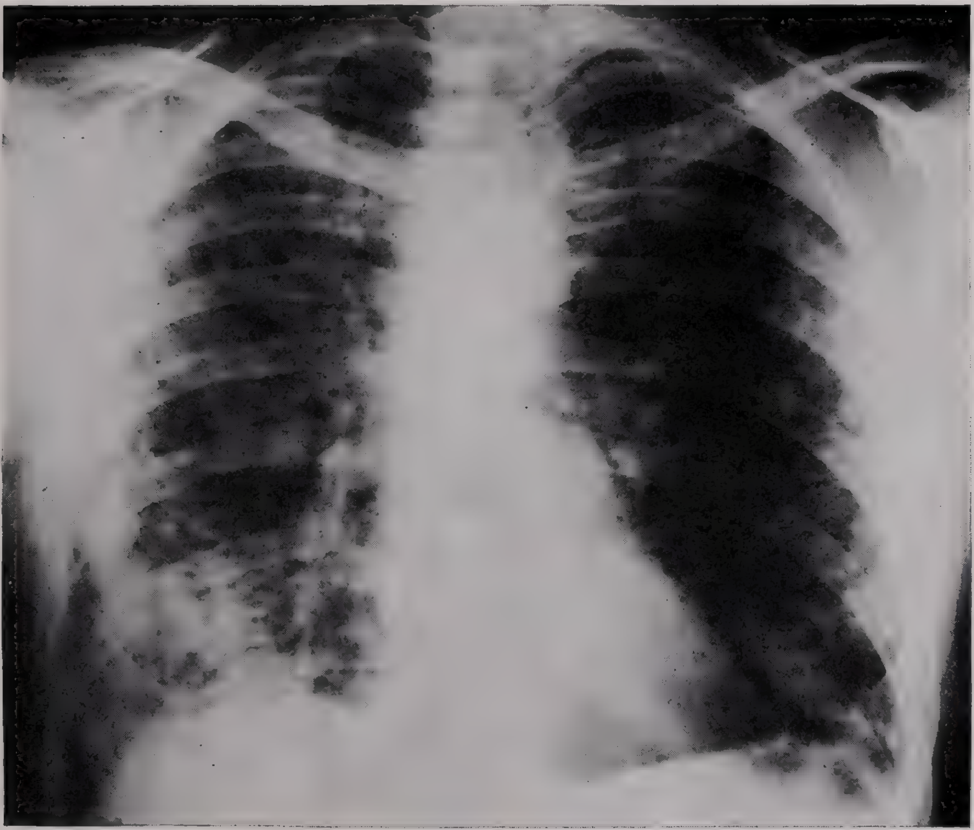
The American Board of Family Practice announces that it will give its FIRST examination for certification in various centers throughout the United States. The examination will be over a two-day period on February 28-March 1, 1970. Information regarding the examination and eligibility for the examination can be obtained by writing: Nicholas J. Pisacano, M.D., Secretary, University of Kentucky Medical Center, Annex #2, Room 229, Lexington, Kentucky 40506.

The Viewing Box

Skin Rash and Abnormal Chest Roentgenogram

THIS IS THE chest film (Figure) of a 22-year-old man who, seven days prior to admission, developed a maculopapular rash on his trunk which soon become vesicular and was accompanied by itching, malaise, dry cough, and pleuritic chest pain.

What is your diagnosis? (See next page.)



Figure

Diagnosis: Chickenpox pneumonia.

The disease varies greatly in severity. At one end of the spectrum it can be severe if not catastrophic and is characterized by dyspnea, hemoptysis, cyanosis, fever, and prostration, while on the other extreme it may be mild, go undetected, and be diagnosed only on x-ray. The disease can be fatal in some cases. Physical findings, even in severe cases, rarely include the classical signs of pulmonary consolidation. Usually there are only coarse breath sounds, occasional rhonchi, expiratory wheezes and tachypnea. Symptoms include cough, hemoptysis, chest pain (50%) of either deep or pleuritic type, dyspnea (50%), fever, and malaise. Laboratory findings are undramatic, consisting of either leukopenia or normal white cell count, occasionally with slight lymphocytosis.

Involvement of the respiratory tract during an episode of chickenpox can be caused by either secondary bacterial invaders or by the chickenpox virus directly. Weinstein and Meade reported a series of 453 patients with chickenpox. Of these, 41 developed respiratory tract infection. Twenty of the 41 were under the age of seven, while 21 were over the age of 19. Children were susceptible to either pure chickenpox or bacterial pneumonitis, the latter most often being caused by *Hemophilus influenzae,* while adults seemed to exhibit exclusively pure viral involvement of the respiratory tract.

X-ray findings: The chest film is characterized by many nodular, rounded infiltrates seen throughout both lung fields. The lesions are variable in size, have indistinct outlines and appear to be concentrated at the lung bases. There is bilateral lymphadenopathy and prominence of the bronchovascular markings. The x-ray changes in the lungs disappear more slowly than the clinical manifestations, some changes persisting up to months or years after symptomatic recovery.

Helmut Behling, M.D.*
Minneapolis, Minnesota

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*Department of Radiology, Hennepin County General Hospital.

References

1. Weinstein, L., and Meade, R. H.: Respiratory Manifestations of Chickenpox: Special Consideration of the Features of Primary Varicella Pneumonia. Arch Intern Med 98:91, 1956.
2. Chickenpox Pneumonia. Brit Med J 2:965, 1966.
3. Sayer, E. N. et al.: Varicella Pneumonia. A report of 20 Cases with Post-mortem Examinations in Six. Calif Med 107:141, 1967.
4. Sargent, Nicholas E., et al.: Roentgenographic Manifestations of Varicella Pneumonia with Post-mortem Correlation. Amer J Roentg 98:305, 1966.

The Golden Age

Devoted physicians also watched over Walt Whitman through the series of cerebral hemorrhages that began in his forties. His Canadian friend Dr. Ralph M. Bucke twice brought the famed Dr. William Osler to see him. Between 1869 and 1888 he suffered four major strokes with paralysis, the last one accompanied by mental confusion and some speech disturbance, but he recovered almost completely from each one, on one occasion after electric stimulation to paralyzed limbs. Autopsy surprised physicians by showing, in addition to longstanding severe cerebral arteriosclerosis, advanced tuberculosis of the lungs and abdomen.*

Editor's Note: Can you imagine William Osler missing a diagnosis like that?

---

*The Patient's Progress, Edited by Felix Marti-Ibanez, 1962.

Nose clear as a whistle

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Dimetapp Extentabs® does an outstanding job of helping to clear up the stuffiness, drip and congestion of colds and upper respiratory allergies and infections. Each Extentab keeps working up to 12 hours. And for most patients drowsiness or overstimulation is unlikely. Try Dimetapp. It clearly works.

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Contraindications: Hypersensitivity to antihistamines. Not recommended for use during pregnancy.
Precautions: Until patient's response has been determined, he should be cautioned against engaging in operations requiring alertness. Administer with care to patients with cardiac or peripheral vascular diseases or hypertension.
Side Effects: Hypersensitivity reactions including skin rashes, urticaria, hypotension and thrombocytopenia, have been reported on rare occasions. Drowsiness, lassitude, nausea, giddiness, dryness of the mouth, mydriasis, increased irritability or excitement may be encountered.
Dosage: 1 Extentab morning and evening.
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Owner Breaks Arm When Yacht Runs Agroun

Schuyler, Oct. 31. Harry Waters of Covesville incurred a fractured arm … acht … ck a large rock … tially capsized. The fire depart had to rescue Waters by small Damage to the yacht is estima

Hasn't the skipper had enough excitement for one day?

For the patient who has been through an accident, the worry and anxiety following the mishap may actually heighten the perception of pain. This is why there's a classic ¼ grain *sedative* dose of phenobarbital in Phenaphen with Codeine—to take the nervous "edge" off, so the rest of the formula can control the pain more effectively.

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Richmond, Va. 23220 A-H-ROBINS

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Phenaphen with Codeine Nos. 2, 3, or 4 contains: Phenobarbital (¼ gr.), 16.2 mg. (warning: may be habit forming); Aspirin (2½ gr.), 162.0 mg.; Phenacetin (3 gr.), 194.0 mg.; Hyoscyamine sulfate, 0.031 mg.; Codeine Phosphate, ¼ gr. (No. 2), ½ gr. (No. 3), or 1 gr. (No. 4) (warning: may be habit forming).

The compound analgesic that calms instead of caffeinates

Indications: Phenaphen with Codeine provides relief in severer grades of pain, on low codeine dosage, with minimal possibility of side effects. Its use frequently makes unnecessary the use of addicting narcotics. **Contraindications:** Hypersensitivity to any of the components. **Precautions:** As with all phenacetin-containing products excessive or prolonged use should be avoided. **Side effects:** Side effects are uncommon, although nausea, constipation and drowsiness may occur. **Dosage:** Phenaphen No. 2 and No. 3—1 or 2 capsules every 3 to 4 hours as needed; Phenaphen No. 4—1 capsule every 3 to 4 hours as needed. For further details see product literature.

Didactic

The Neurological Examination*

THE NEUROLOGICAL examination is a gross but useful tool, without mysticism or ritual. It is a method of challenging the function of the nervous system and/or its parts. If the nervous system meets the challenge of a normal response to a neurological examination it is assumed to be reasonably healthy; if it fails it is likely to be pathological. Authors have devoted much energy and many pages to describing the subtleties and endless techniques of the examination until many are convinced that it is an impossible task. The purpose of this paper is to dispute this impression. Much information is available from the neurological examination and all practitioners are fully able to perform and interpret it most adequately in their practices.

Organ Function

We should always start our neurological examination by challenging the "organ function:" the total brain function consisting of awareness of time, place, person and changes in the environment. Decompensation of this function results in disorientation, confusion or coma.

Orientation

The most clinically useful "organ function" is orientation, and it is the most frequently neglected sign. The individual who errs in his orientation of time, place or person has significant diffuse involvement of his entire brain. Less extensive diffuse pathology of the entire brain manifests as impaired memory, either recent or remote, impaired judgment and impaired mental capacities.

Focal Pathology

Each brain hemisphere contains a motor, a sensory, and a visual function and, uniquely to the left hemisphere is the speech function.

Frontal Lobe

The anterior 70% of each hemisphere is the frontal lobe which has a motor function. Pathology here manifests as a contralateral upper motor neuron deficit of the face and/or the extremities. A central seventh paresis, a loss of a nasolabial fold and a slight loss of mobility of the facial musculature below the eye, or a minimal motor deficit of the twelfth cranial nerve with slight deviation of the protruded tongue away from the side of the lesion suggests a lesion involving the corticobulbar tracts of the frontal lobe. A loss of volitional movement, a hyperreflexia, an increase in tone (spasticity), a sustained or unsustained clonus or the appearance of asymmetric pathological toe signs on one side signifies pathology within the contralateral corticospinal tracts of the frontal lobe.

Thalamoparietal Region

The thalamoparietal region of the hemisphere functions to permit awareness of sensory stimuli from the contralateral side of the body. Pathology here results in a loss of awareness of sensory appreciation. Lesions within the thalamus produce a hypalgesia and hypesthesia of the contralateral side of the body and face often including the cornea, and the pharyngeal wall. The deficit may be gross as compared to the more normal side or it may be subtle, manifest only as a neglect of the side when simultaneous bilateral stimulation is performed.

Parietal Cortex

The function of the parietal cortex is to reach conclusions. Pathology here may make it impossible for the brain to utilize the sensory cues of the size, shape, texture and weight of an object in order to identify it correctly. This is how we utilize astereognosis.

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*Presented before the Minnesota Academy of General Practice Convention, Hotel Radisson, Minneapolis, Minnesota.

Occipital Lobe

Posteriorly the occipital lobe receives fibers from the eye via the thalamus which carry visual cues. Pathology involving these fibers (geniculo-calcarine tract) results in an impaired appreciation of visual clues entering the eye from the opposite side of the body. A lesion involving the temporal lobe portion of these radiations results in blindness to cues from the contralateral superior quadrant of each field of vision. A lesion of the parietal lobe may result in blindness to cues from the inferior quadrants. A lesion of the geniculate portion of the thalamus or at the occipital pole produces blindness from the entire contralateral half of visual fields of each eye. These deficits can be easily determined on tangent screen examinations and their pattern permits precise localization of pathology.

Speech Center

Speech is the fourth clinical function of the brain and is uniquely vulnerable in the left hemisphere alone, especially the posterior one half. Lesions within the left hemisphere produce aphasia. Lesions posterior in the temporoparietal-occipital region may impair the appreciation of the spoken word or the formulation of appropriate speech. Appreciation of simple directions may be lost; or the ability to recognize and name objects, words, figures and body parts correctly is lost. Speech produced, though erroneously, is not appreciated by the brain and there may be no effort to correct it. Lesions more anterior in the isthmus of the temporal lobe or the frontal lobe speech center may result in near total inability to speak, a deficit so recognizable by the brain that the patient manifests obvious severe frustration. Hence normal or abnormal speech tells us much about the state of the brain.

Cerebellar Structure

Coordination

Another important function, coordination, is vulnerable in the cerebellar structure. Lesions within the mesial structure produce a staggering, inebriated gait characterized by the feet being placed wide apart; sudden turns are unsteady. These signs appear when pathology develops in this portion of the cerebellum. Other than the primary function of maintaining a coordinated upright gait, the cerebellar hemisphere coordinates the movements of the arms and hands. Pathology here causes gross tremor near the completion of a motor act of the ipsilateral hand (an intention tremor) seen as the hand tries to touch the nose. Lesions here impair the ability of the extremity to measure its movements accurately and result in "past pointing" or "overshooting the mark" on attempted tasks. The capacity to do rapidly alternating movements of the ipsilateral hand may be impaired from pathology in this portion of the cerebellar system.

Brain Stem

Midbrain—Pons

The brain stem of man is a very small structure that controls the muscles of the face and head region. The functions of the brain stem express themselves externally on the ipsilateral side and are discretely manifest in movements that are simple to test. The function of the midbrain from a clinical standpoint is movement of the ipsilateral eyeball upward, downward and nasally. The pons' functions are to close the jaw, turn the ipsilateral eye laterally, and move the facial muscles. A manifest unilateral deficit of lateral rotation of the eye, of contraction of the masseter muscle or the facial musculature is evidence of pathology within the ipsilateral pons.

Medulla

The function of the medulla, the lowest portion of the brain stem, is to permit swallowing and speaking, movement of the tongue and regulation of the cardiorespiratory rate. Focal pathology within this structure manifests as an ipsilateral flaccid paresis of the palate or atrophy and paresis of the tongue. The vital regulatory functions of heart and respiration are less vulnerable and clinically of little significance in the neurological examination.

Basal Nuclei

The extra-pyramidal functions of motor tone and movement regulation come from the deep midline paired basal nuclei. Abnormal movement of choreic, athetoid,* ballistic, dystonic or tremor type warrants the conclusion that these structures are pathologically involved. "Cogwheel" rigidity is produced by pathology in these same structures.

Spinal Cord

The spinal cord functions as a simple carrier of information to and from the higher centers. It is also the origin of the final common pathway to the musculature of the body and organs. This final common pathway originates in the anterior horn cell column which has a reliable longitudinal distribution in relation to body musculature. Each level of the cord innervates a definite muscle group in a way which permits the neurological examination to localize precisely within it.

Upper Three Cervical Segments

The function of the upper three segments of the cervical cord is flexion of the chin upon the chest; loss of the sternocleidomastoid mass or power on one side denotes pathology of the ipsilateral cord at that level.

Fourth Cervical Segment

The function of C_4 level is control of the diaphragm; its paralysis with a resultant loss of cough is a manifestation of pathology at this level.

Fifth and Sixth Cervical Segments

The function of C_5–C_6 is to innervate the biceps of the ipsilateral arm; flaccid paresis or atrophy of this muscle pointedly suggests pathology of the cord.

Seventh and Eighth Cervical Segments

C_7 functions to flex and extend the wrist; a loss of these functions alone localizes the pathology to that level. Cervical levels 7 and 8 distribute to the triceps of the ipsilateral arm; loss of elbow extension power or atrophy, fasciculations or hypoflexia of that muscle warrants the conclusion of pathology at that level. The levels of C_8–T_1 function to give us power of hand grasp; pathology at that level results in a loss of grip.

Summary

Thus the purpose and partial technique of the neurological examination as herein outlined constitutes a method of evaluating the status of the central nervous system by challenging the various functions of the parts. A few very simple tests give us much useful information and permit us to derive accurate conclusions about the health or disease of the nervous system.

George C. Flora, M.D.†
Minneapolis, Minnesota

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*See Test Your Word Score Page 1761.

†Associate Professor of Neurology, University of Minnesota Medical School, Minneapolis, Minnesota.

Donald A. Scholz, M.D.

Dr. Scholz is a consultant in internal medicine on the staff of the Mayo Clinic where he subspecializes in endocrinology.

The photograph of Taxco, Mexico, was taken in August, 1968, from a vantage point which looks down on the city and across the valley.

Dr. Scholz was a snapshot winner in the Annual Minnesota Sunday Tribune contest in 1963, with a certificate of merit from the National Newspaper Contest when the picture was submitted that same year.

Selfishness

A farmer imported some especially fine seed-corn and produced a crop that was the envy of his neighbors. When they sought some of the seed, he refused, fearing to lose the competitive advantage he had gained. The second year his crop was not so good; the third year, results were even worse. Suddenly, it dawned upon him that the poor-grade corn of his neighbors was pollinating his prize corn. His selfishness had caught up with him.

Business Efficiency

Abstracts

ABDOMINAL ADENOVIROSIS AND APPENDICITIS

Doctors Bonard and Paccaud[1] have demonstrated adenoviruses in appendices and in abdominal lymph nodes of patients with mesenteric adenitis. These patients, who ranged in age from two to 22 years, had a laparotomy for acute appendicitis. The authors studied 158 specimens: 26 appendices, 59 lymph nodes, and 73 mixed specimens made up of an appendix and an abdominal lymph node. All specimens were minced and cultured on coagulated chick plasma medium. Adenoviruses were isolated from 11.7 per cent of the appendices, 3.8 per cent of the lymph nodes, and 17.7 per cent of the mixed specimens. Types I, II, and VII adenoviruses were cultured out. Feces cultures yielded no viruses.

Microscopically, two appendices showed acute inflammation, whereas the others exhibited chronic, slight inflammation to none. All lymph nodes were swollen and showed adenitis (hyperplasia). Bonard and Paccaud divide mesenteric lymphadenitis into two phases. Phase I is characterized by acute abdominal pains and signs of recent viral disease (upper respiratory tract); it may or may not be complicated by an acute appendicitis. During this phase of viremia lymph follicles of the ileum, appendix and mesentery lymph nodes may become infected. The complement fixation test is positive and isolation of adenoviruses can be accomplished. Phase II is characterized by chronicity. The adenoviruses remaining in the cells elicit no detectable immunological reaction. Abdominal virus adenitis should be considered when a patient presents the following syndromes: pharyngitis, even mild, pains in the right iliac fossa, either chronic or acute with an exacerbation, contemporary to the pharyngitis.

Of 15 patients studied by Bonard and Paccaud, seven complained of abdominal pain of varying intensity for several weeks previous to hospitalization. In eight patients, the onset was acute and indistinguishable from acute appendicitis. Because of the clinical difficulty of distinguishing between these two clinical entities, Bonard and Paccaud recommend that all patients with acute right fossa pains should have a laparotomy whether or not they have a recent history of a viral infection. They advance the postulate that inflammatory lesions in the submucosa may play a role in certain types of acute appendicitis. As long as the mucosa is intact, the appendix may be only slightly hyperemic. When the mucosa is destroyed, however, bacterial superinfection may occur, resulting in an acute appendicitis.

Emil Maro Schleicher, Ph.D.
Minneapolis, Minnesota

Reference

1. Bonard, E. C., and Paccaud, M. P.: Abdominal Adenovirosis and Appendicitis. Helvetica Medica Acta 33:164, 1966.

A split atom and a split mankind cannot co-exist indefinitely on the same planet.
—Liston Pope

The best boss doesn't boss; he inspires.—A. Dodds.

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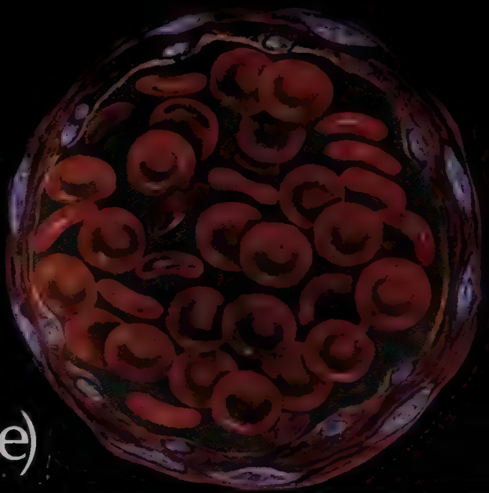

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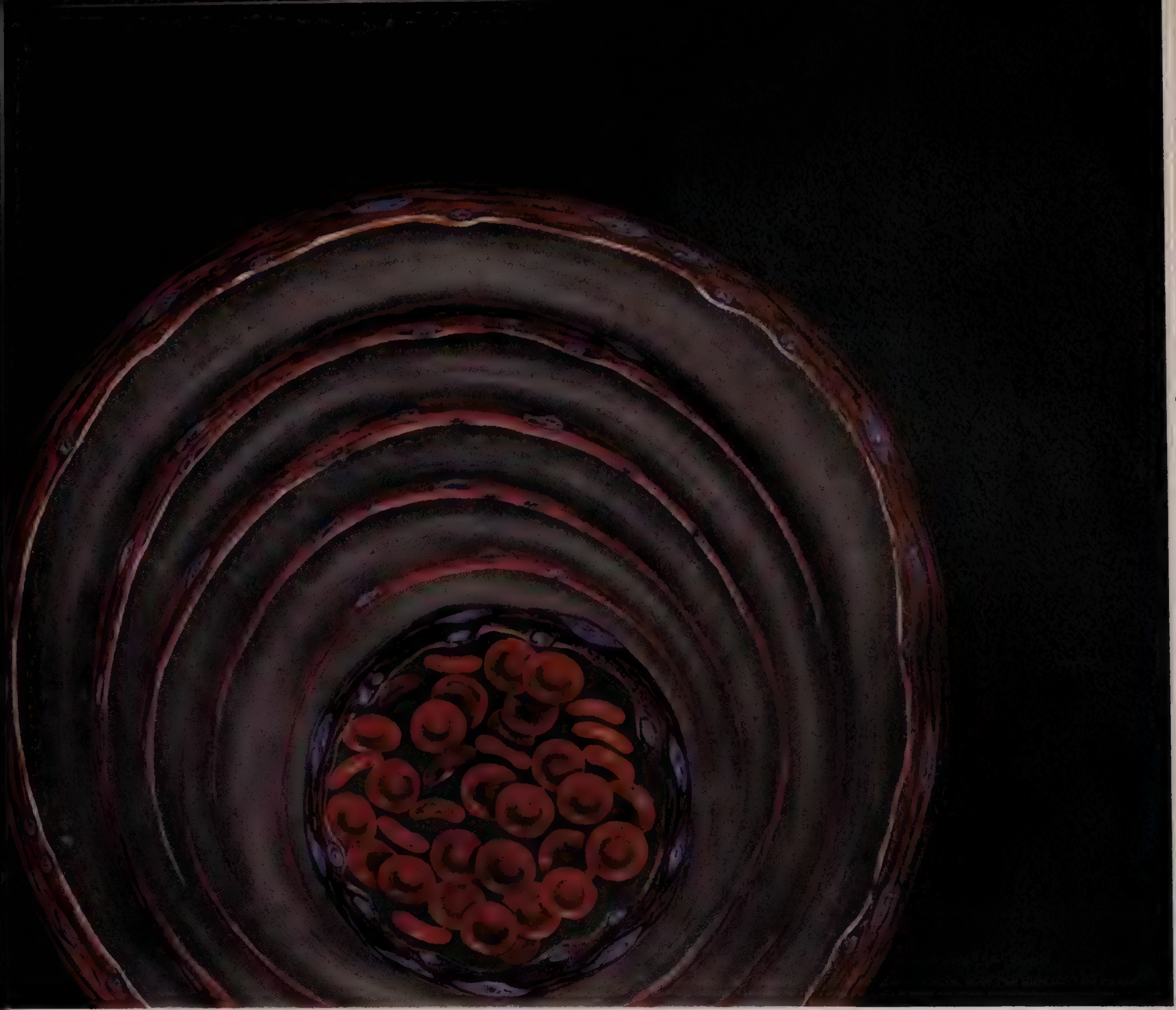

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(Continued to Page 1800)

Fracture Conference

Some Complications of Hip Fractures*

Joseph M. Janes, M.D.:†

The first case is that of a 46-year-old woman who came to the Mayo Clinic on January 10, 1968. She had fractured the left femoral neck in June of 1967 and, although she had been allowed partial weight-bearing at home, she continued to have pain (Figure 1). The lateral roentgenogram in this case showed that the nail was not in the neck. The neck of the femur had been partially absorbed. I thought the femoral head might be viable, and I considered doing a McMurray osteotomy (Figure 2), but some of my colleagues thought that the femoral head was probably not viable. At operation it appeared not to be. What would your impression be in this case?

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*Fracture Conference, June 17, 1968.
†Section of Orthopedic Surgery.

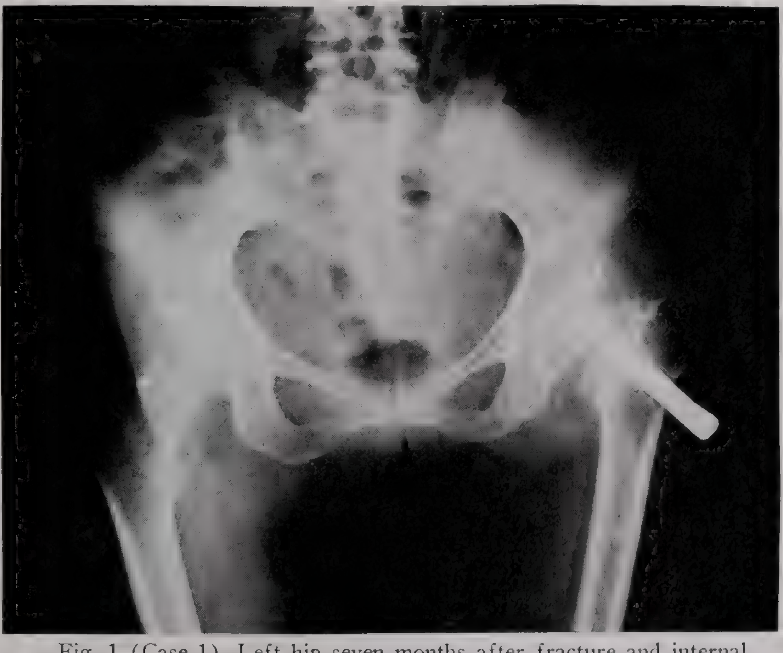

Fig. 1 (Case 1). Left hip seven months after fracture and internal fixation. There is nonunion of fracture. Head of femur is loose, and neck has slipped anteriorly and superiorly.

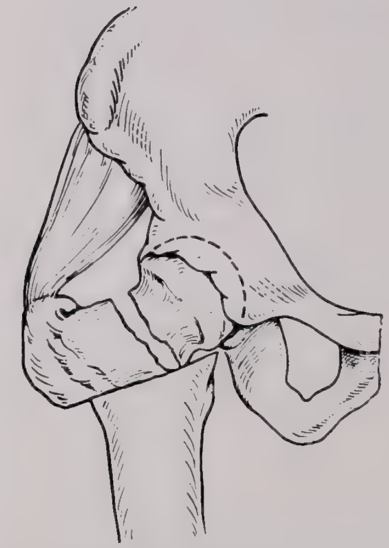

Fig. 2. McMurray osteotomy. (From Colonna, P. C.: Regional Orthopedic Surgery. Philadelphia, W. B. Saunders Company, 1950, p. 326. By permission.)

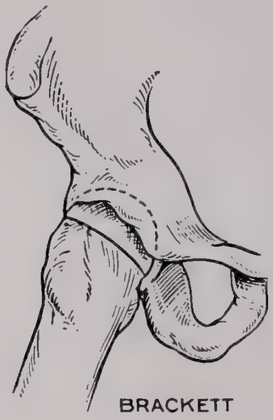

Fig. 3. Position after Brackett procedure. (From Colonna, P. C.: Regional Orthopedic Surgery. Philadelphia, W. B. Saunders Company, 1950, p. 327. By permission.)

Patrick J. Kelly, M.D.:*

Well, let us take the point of view that maybe all femoral heads are not viable when there is no union in such a fracture; if you could trim enough dead bone away from the head, you could then do a Brackett procedure (Figure 3) which I have done in one or two cases in which the femoral head did not bleed well at operation. The patients have subsequently done quite well.

Dr. Janes:

Has the Brackett procedure been compared with the Austin-Moore procedure for this type of thing?

Dr. Mark Coventry:*

No. Dr. Donald Webb and I have just gone over the cases in which I have done the Brackett operation, and the Moore prostheses have been pretty well evaluated. I do not think we could ever come up with a reliable comparison of the two. Age, general health, the amount of femoral neck remaining and the general appearance of the head—all of these points and others make each problem an individual one. I think this might be a better case for a Brackett procedure than for an osteotomy because of the lack of a femoral neck and because of the peculiar change inferiorly on the medial surface. Also, one hates to put a prosthesis in a 46-year-old person.

Dr. Janes:

I have not done so many prostheses for patients less than 50 years old, but we did, in fact, use a prosthesis in this case (Figure 4). I think the Brackett procedure is a technically more complex operation than inserting a prosthesis.

Dr. Janes:

The patient came back to see us in April, at which time she was allowed to bear weight with the support of a cane. She had no pain.

Einer W. Johnson, Jr., M.D.:*

Perhaps, Dr. Janes, it should be said that, although you did not know in this instance whether the head was viable, you decided to do the prosthesis, and at the time of operation you found that the head was not viable. As a routine, what would you think about doing tomograms, assuming, as in the previous case, that we do not know if the head is dead or alive? What is your view on tomograms?

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*Section of Orthopedic Surgery.

Dr. Janes:

That is exactly what we did in the next case.

Viability of the Head

A 68-year-old woman slipped and fell in December 1966. At her home hospital she had the fixation shown in Figure 5. She continued to have pain.

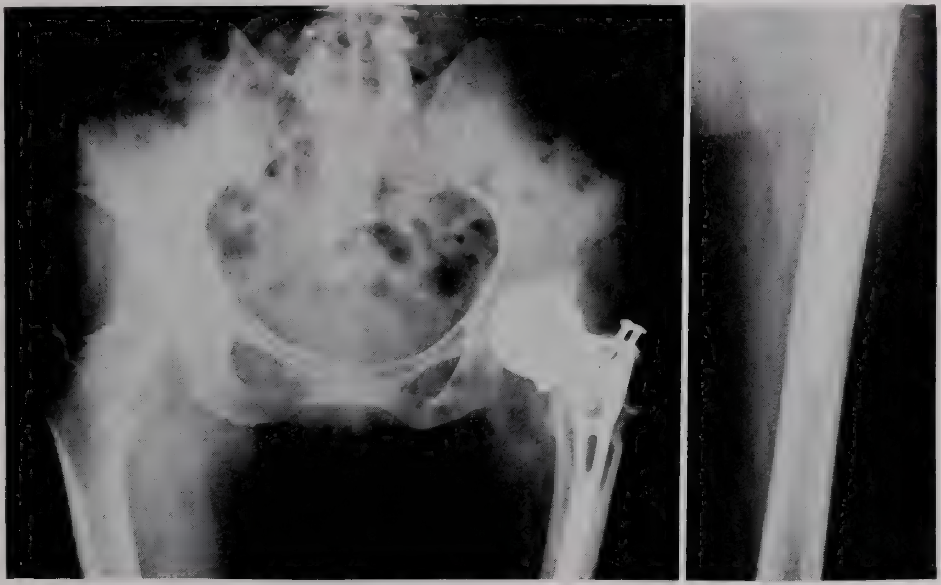

Fig. 4 (Case 1). Three months after removal of nail and insertion of prosthesis.

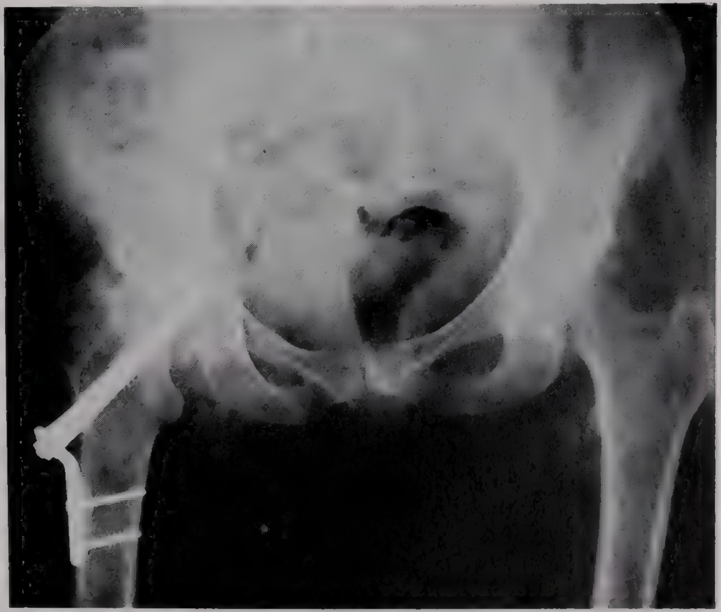

Fig. 5 (Case 2). One year after fracture and internal fixation of right hip. Note collapse of neck, penetration of acetabulum, and resorption about nail. Plate prevents nail from backing out despite resorption.

One can see that she had a graft as well as the fixation. Bone for the graft apparently had been taken from the femur just below the shank of the nail. Thus, the surgeon in this case was trying to take every precaution to prevent what happened. I think the nail would have been fine without the shank which may have been responsible for the pain in the groin that actually brought the patient to us.

Dr. Coventry:

I think part of the head is avascular. Dr. Kelly and I apparently disagree a little on this, but I do not think one could say the *whole* head is vascular or the *whole* head is not vascular. I think the point in the superior aspect of the femoral head is avascular, and I think the point adjacent to the nail and inferior is vascular.

Dr. Janes:

Thank you. We had tomograms in this case (Figure 6). They reportedly showed "no convincing evidence of nonunion" and "no evidence of avascular necrosis."

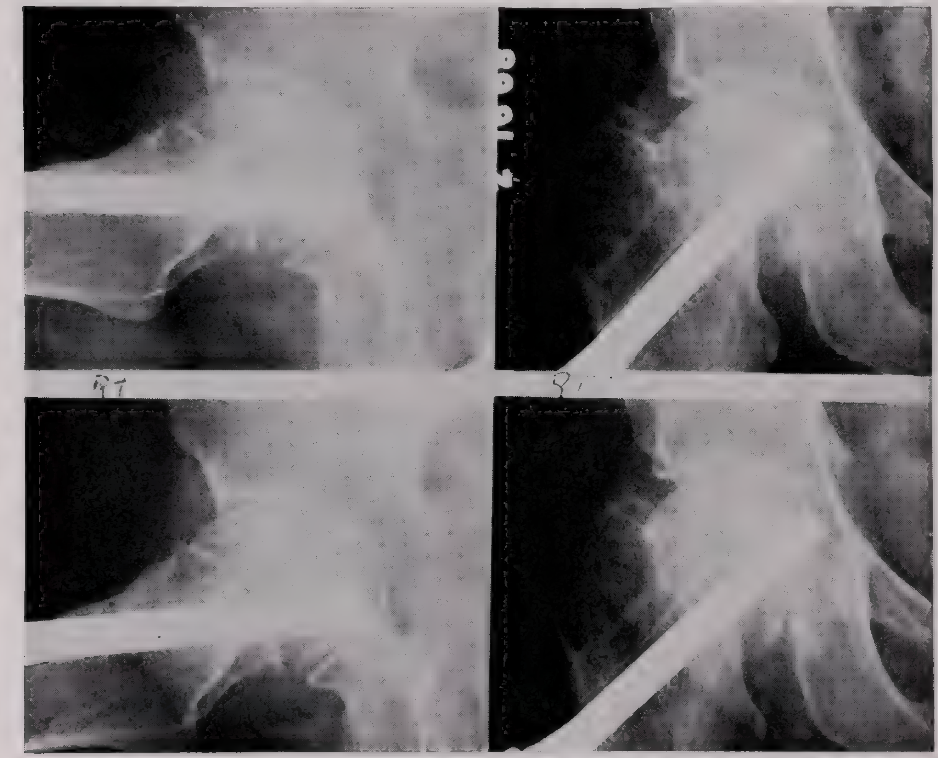

Fig. 6 (Case 2). Tomograms showing no definite evidence of avascular necrosis or nonunion.

Dr. Coventry:

The conical area that I pointed out certainly shows beautifully on the tomograms.

Dr. Janes:

Dr. Johnson, do the tomograms help you in this instance?

Dr. Johnson:

Yes. I agree with Dr. Coventry; I think the femoral head is half dead and half alive.

Dr. Coventry:

One third and two thirds?

Dr. Janes:

I thought she might do well because the roentgenologic report said that there was probably union and no convincing evidence of avascular necrosis.

Dr. Janes:

I took out the internal-fixation nail and found avascular necrosis right where the graft was (Figure 7). A prosthesis was substituted (Figure 8) and the patient is now at home using crutches. She is to avoid weight-bearing for three months.

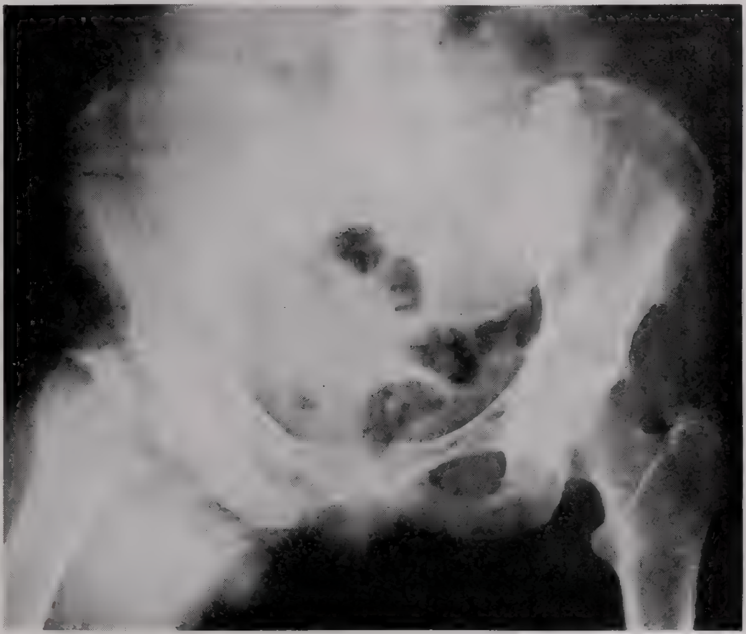

Fig. 7 (Case 2). Obvious nonunion. Femoral head appears to be necrotic.

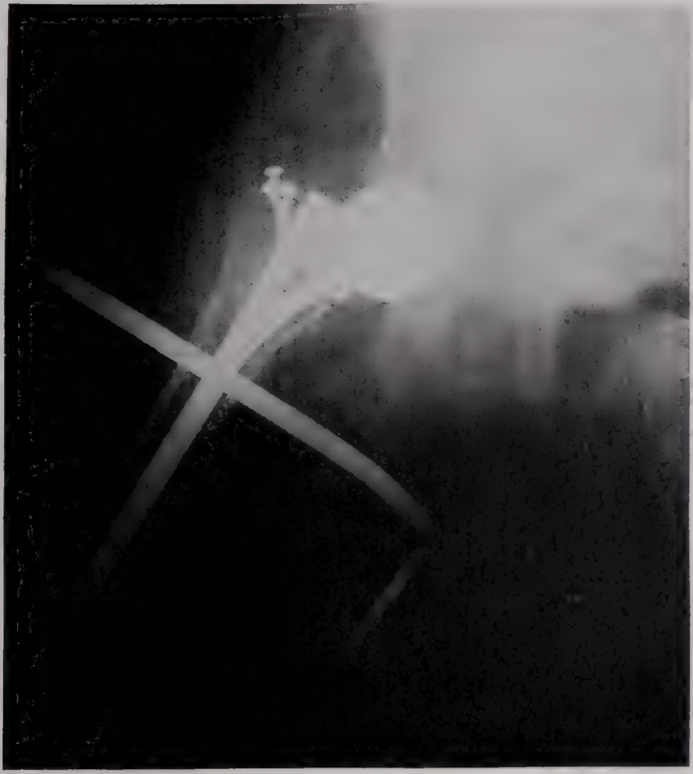

Fig. 8 (Case 2). After insertion of prosthesis.

Dr. Coventry: Dr. Janes, what did you think about the vascularity of the head when you took it out?

Dr. Janes:

It was mainly avascular. There were some bleeding areas, but the most avascular part was that where the cortical bone graft had been applied—which is not supposed to be the case.

From a practical standpoint, however, if there is any avascular necrosis at all, is that not all you need?

Dr. Coventry: That depends on where it is. Certain small areas of avascular necrosis will not interfere with function and may even regenerate and revascularize in time. Unfortunately, it is usually the superior weight-bearing surface that is avascular and that is just the part one does not want affected.

Persistent Pain

Dr. Janes:

The next case concerns a 66-year-old woman who tripped on a rug in church and fractured her right hip in October 1964. Knowles' pins were inserted and a year later were removed. The patient had persistent pain and had not walked without support since the fracture. In October 1966 she had an operation elsewhere for the insertion of a prosthesis (Figure 9). An acetabuloplasty was done at the same time. The patient continued to have pain and came here in February 1968. She was on crutches and unable to bear weight on the right foot.

Dr. Coventry: Marked osteoporosis is surely evident.

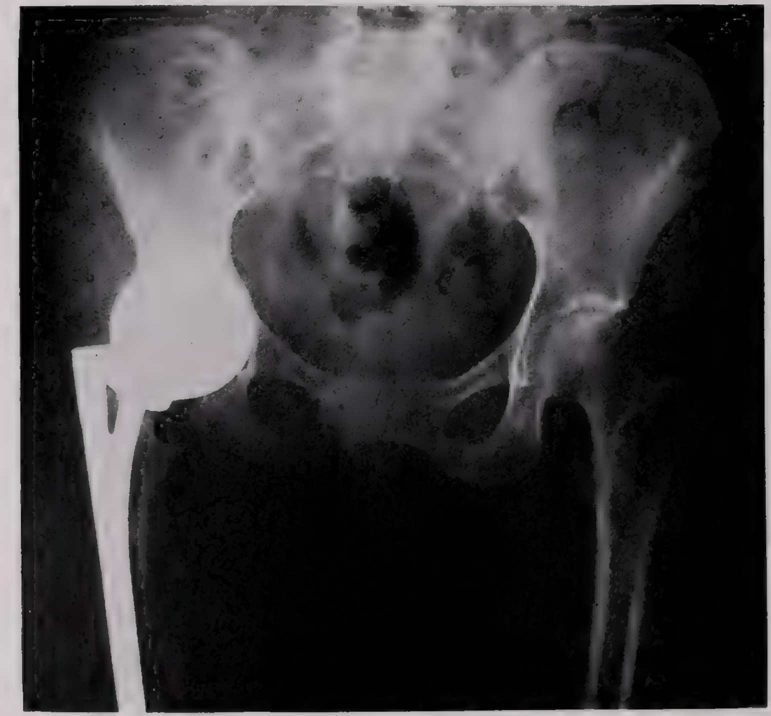

Fig. 9 (Case 3). Appearance of prosthesis for right hip one and three-quarters years after its insertion.

Emanuel Semerad, M.D.:*

The prosthesis is extremely large. The inner wall of the acetabulum has remodelled itself around the prosthesis.

Dr. Janes:

One cause of a painful hip is too large a head on the prosthesis. I cannot quite explain why that is; the lady said she had the acetabulum reamed out so they could put that in. Can you tell me another cause of pain in the hip associated with a prosthesis?

Ray E. Santos, M.D.:*

Dislocation could be another cause. Infection is another; loose prosthesis is another.

Dr. Janes:

Another one?

Allen P. Schlein, M.D.:*

Retroversion or anteversion of the head of the prosthesis.

Dr. Janes:

I think there is a large group where everything looks fine and the roentgenograms look good, but the patient has pain.

Dr. Coventry:

There is another circumstance called the "sinking" prosthesis and it is just the opposite of the acetabular-protruding prosthesis. Instead of going up into the pelvis, it sinks down the shaft of the femur.

Dr. Janes:

If this prosthesis is not quite right, do you think putting another prosthesis in is the answer?

Dr. Schlein:

I think you would probably run into trouble with another one. This one is nowhere near the size of the opposite femoral head. This looks massive. I

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*Resident in Orthopedic Surgery.

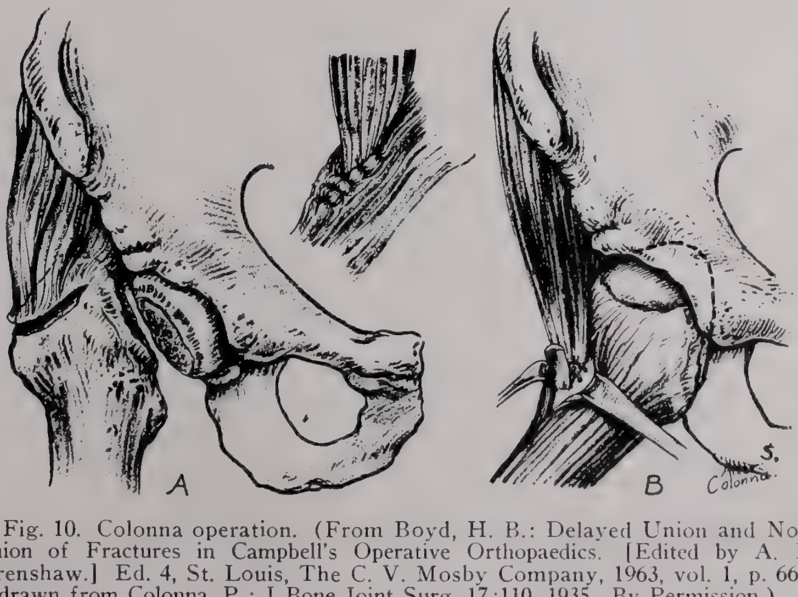

Fig. 10. Colonna operation. (From Boyd, H. B.: Delayed Union and Nonunion of Fractures in Campbell's Operative Orthopaedics. [Edited by A. H. Crenshaw.] Ed. 4, St. Louis, The C. V. Mosby Company, 1963, vol. 1, p. 669; redrawn from Colonna, P.: J Bone Joint Surg. 17:110, 1935. By Permission.)

do not think another prosthesis is the answer. I think you have to do one of the other procedures. I would hate to tell you to arthrodese this hip for a 66-year-old woman, but at least you could get rid of her pain by this operation.

Dr. Janes:

This is one of the procedures that we considered—to put bone grafts around the hip prosthesis. We also thought of the Colonna procedure and finally, after much soul searching, we did a Colonna operation (Figures 10 and 11). We left the patient in the cast six weeks, kept her in bed another week or so and encouraged her to mobilize on her own. She was relieved of her pain and dismissed on crutches with instruction to have a lift put on her shoe. I recently heard from her doctor, and he said that she still has no pain.

Dr. Coventry:

We have had about 12 dislocations of the prosthesis in our series. In the Colonna procedure the lesser trochanter acts as a fulcrum against the side of the pelvis if the acetabulum is too high, as it was here. The Colonna procedure is a much better operation than a pure Girdlestone (Figure 12)—if you

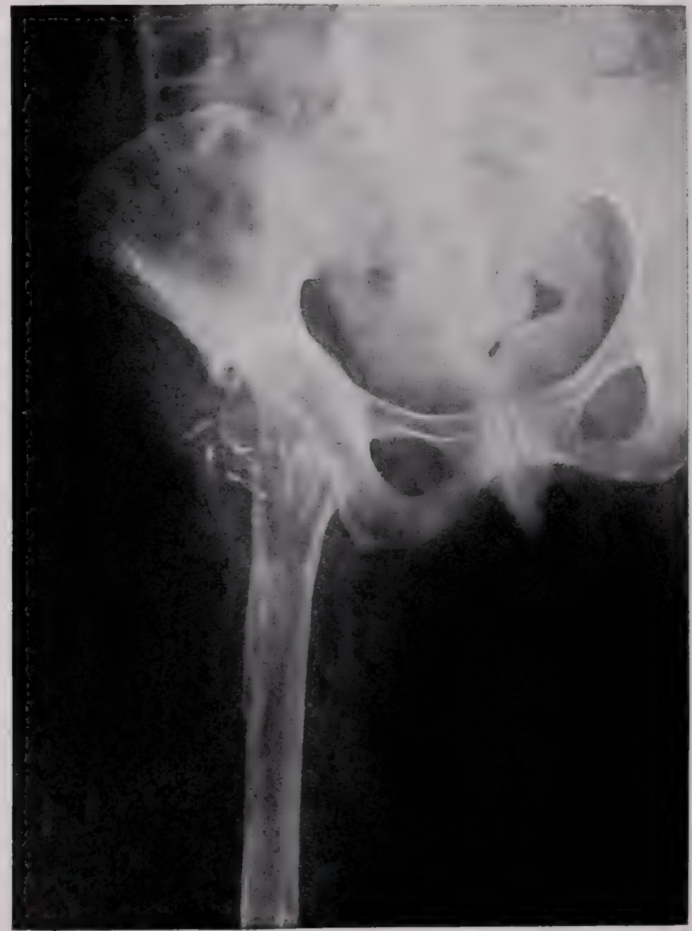

Fig. 11. (Case 3). Two months after removal of prosthesis and Colonna reconstruction of hip.

can get by with it—because there is less shortenting, and one has stability.

Infection

Dr. Janes:

Our next case is that of a 66-year-old woman who fell on the ice and fractured her hip in December 1957. The fracture was nailed in her home community. The nailing failed, and a prosthesis was inserted in June 1958. Two months later purulent material drained from the hip and continued as a sinus until April 1963 when incision and drainage was done; but drainage resumed. The patient came to this clinic in October 1963. The prosthesis was in place (Figure 13), but she complained of a painful hip. We removed the loose prosthesis, which we thought was promoting further drainage, and did a Colonna procedure (Figure 14); and her wound was packed open until it healed from the base. The patient was in a cast for six weeks and later dismissed on crutches. She came back here in May 1964 with no drain-

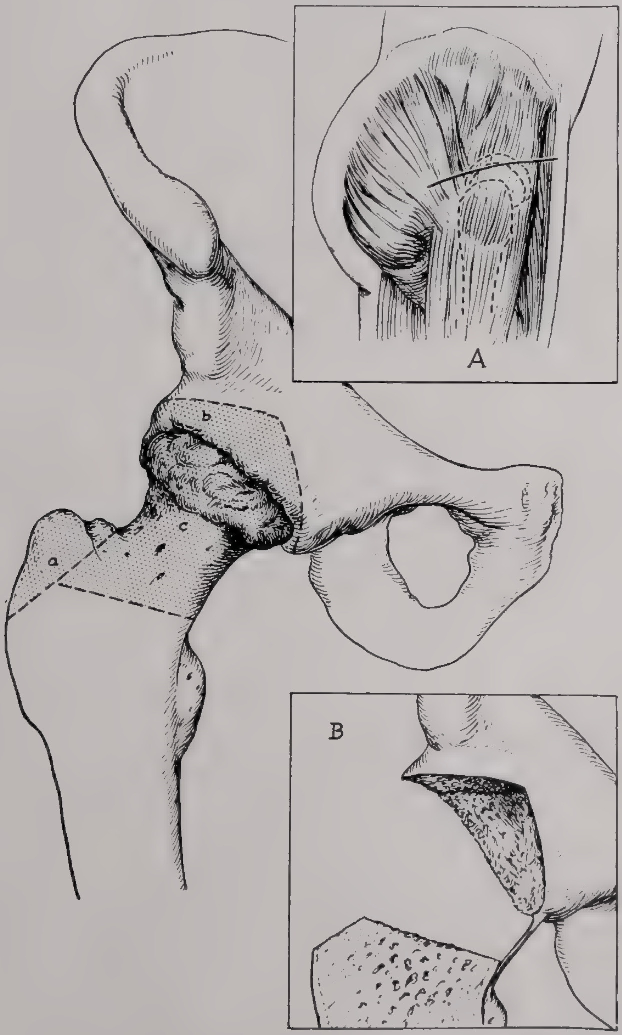

Fig. 12. Girdlestone operation. (From Waring, T. L.: Acute Infectious Arthritis and Wounds of Joints. In Campbell's Operative Orthopaedics. [Edited by A. H. Crenshaw.] Ed. 4, St. Louis, The C. V. Mosby Company, 1963, vol. 1, p. 847. By permission.)

age. Roentgenograms taken then show that if the head had not dislocated it certainly was on the edge of the acetabulum (Figure 15).

Dr. Johnson:

What about her pain? Did she get an acceptable range of motion?

Dr. Janes:

She did not get return of a full range of motion, but she lost most of her pain. She was happy. I suppose we could have treated the infection by continuous suction and by using irrigation tubes rather than packing the wound open.

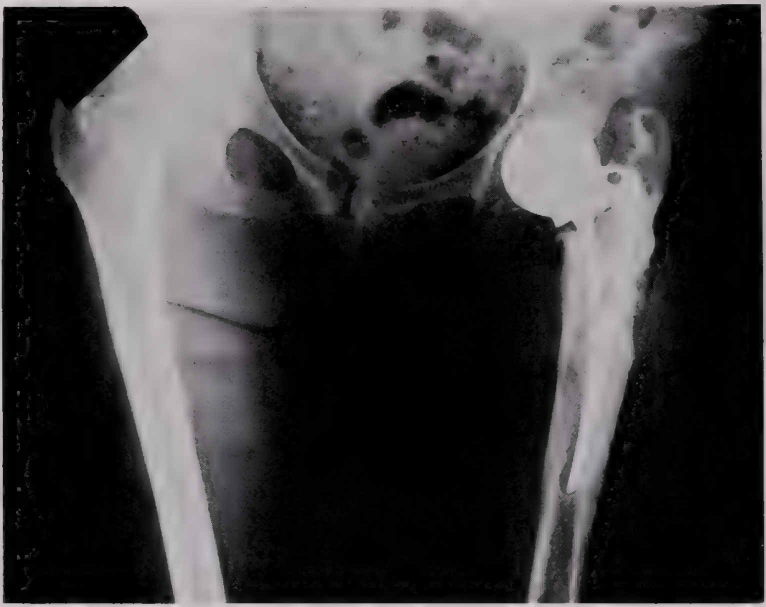

Fig. 13. (Case 4). Five years after insertion of prosthesis for nonunion of fracture of left hip. Note resorption of bone about stem of prosthesis and wide joint space.

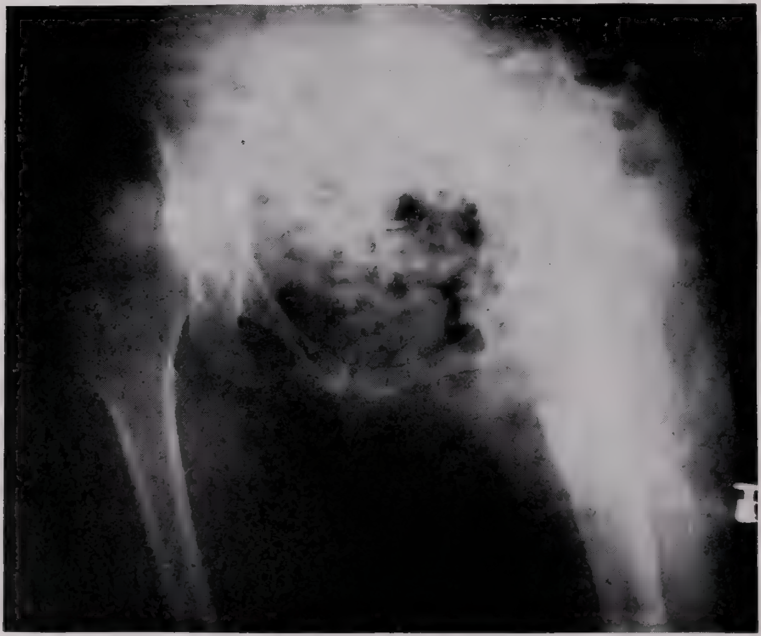

Fig. 14. (Case 4). One month after removal of prosthesis and Colonna reconstruction of hip.

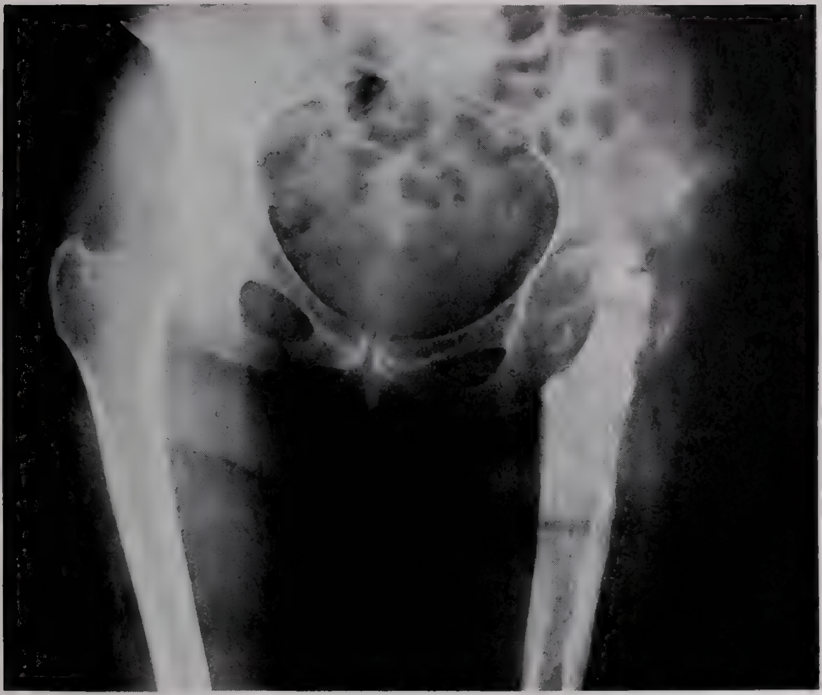

Fig. 15. (Case 4). Partial dislocation seven months after Colonna operation.

Wobble of the Prosthesis

Dr. Janes:

The last case is that of a 62-year-old woman who complained of a painful hip when she came to this clinic in November 1967. She had been operated on by one of our former residents. He had used a staple to hold a portion of the trochanter in place (Figure 16). She gave the history that postoperatively, while she was in a department of physical medicine elsewhere, she slipped and injured her hip. Whether this has any significance, I do not know. Would someone venture to say why this hip was painful?

Dr. Noel T. Van Ness:*

She has very little femoral neck left, which could cause some problems. I get the impression that there is an area of resorption around the end of the prosthesis which would indicate that it was loose.

Dr. Janes:

The diagnosis was made a little easier in this case because the patient said that when she put her weight on this leg she could feel something clicking in her hip.

I have usually gone on the principle that if one prosthesis has failed there is not much reason to believe that a new prothesis will do any better. But that is probably not a completely valid assumption, especially if it is a longer-stemmed prosthesis which we have available now. In this case, we did insert a different type of prosthesis (Figure 17), but we also did something else. We inserted iliac grafts to further strengthen the area of contact of the prosthesis. This patient was last seen in March 1968. I think you can observe that the iliac grafts appear to have consolidated (Figure 18).

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*Resident in Orthopedic Surgery.

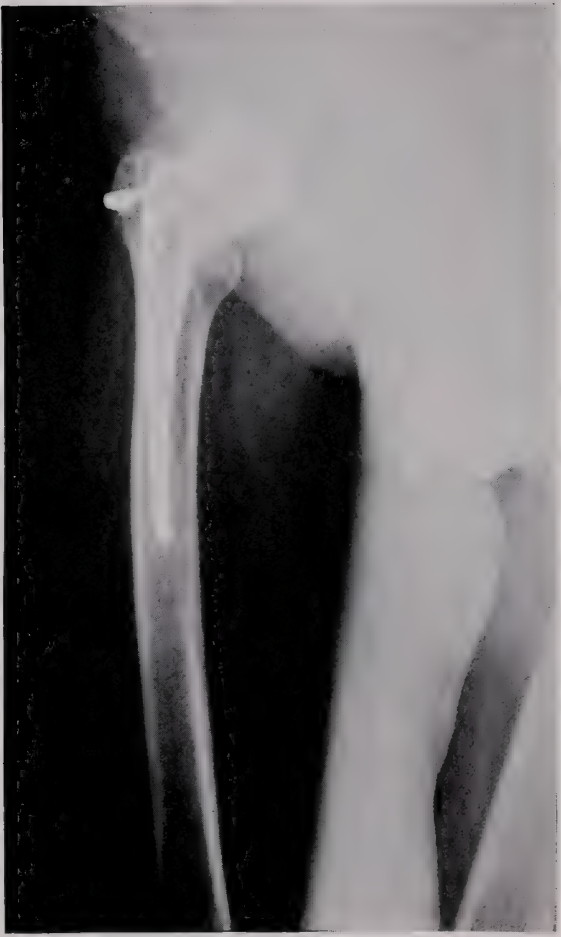

Fig. 16. (Case 5). Resorption of bone about stem of prosthesis of right hip one and a half years postoperatively.

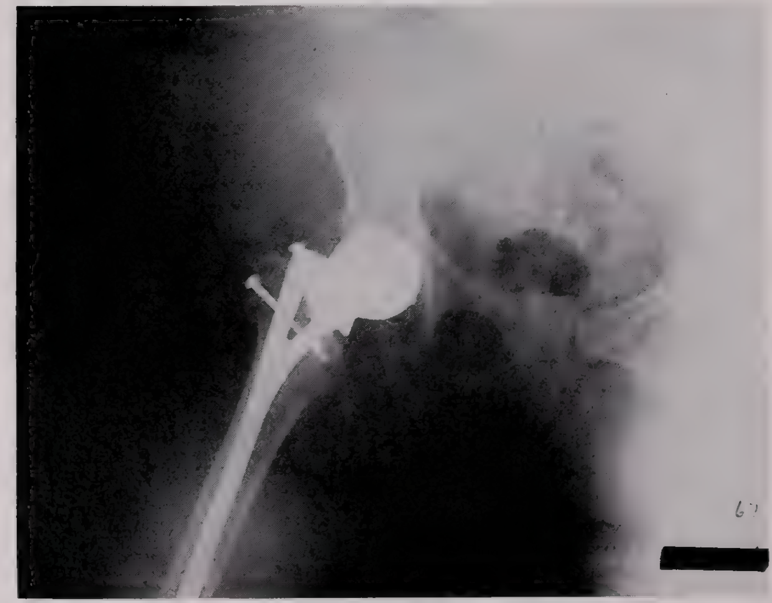

Fig. 17. (Case 5). After insertion of Matchett-Brown prosthesis **and** application of iliac grafts to medullary cavity of femur.

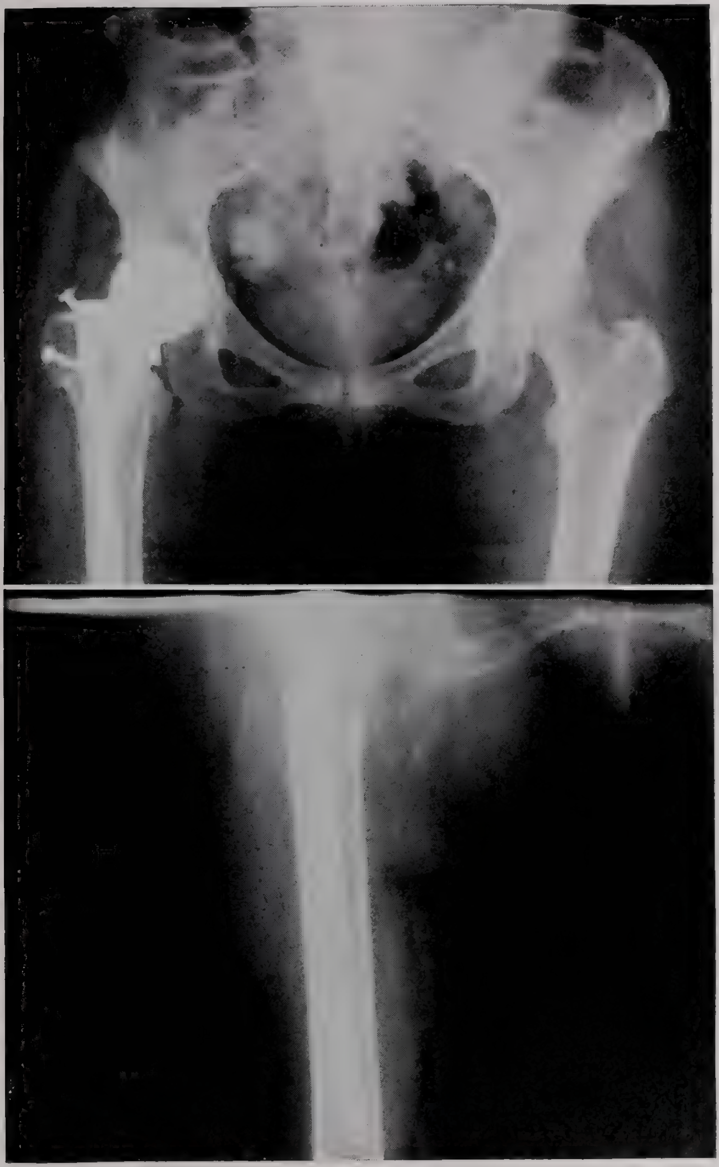

Fig. 18. (Case 5). Six months postoperatively.

I usually allow the average prosthesis patient to bear full weight after three months, but in this case I suggested that the patient stay on crutches for another two months. She was bearing weight on the right leg at time of follow-up.

In summary, these cases illustrate very well the statement that fracture about the hip is "an unsolved problem." Avascular necrosis of the femoral head, nonunion, resorption of the femoral neck, malunion of the fracture—all are complications that must be reckoned with. And often the measures taken to combat these complications carry with them another group of complications as the final two cases illustrate. Graft these problems onto a patient of advancing age and it is easy to understand why and how these problems become a real challenge to all doctors concerned with the treatment of such fractures.

Joseph M. Janes, M.D.*
Ronald D. Suiter, M.D.*
Einer W. Johnson, Jr., M.D.*
Rochester, Minnesota

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*From the Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

Classified Advertisements

Continued from page 1786.

GP AND OB GYN wanted to join two GPs, surgeon, and internist in suburban group. Excellent nearby hospital. Salary first year, then partnership. Write MINNESOTA MEDICINE-436, 375 Jackson, St. Paul 55101.

GENERAL PRACTITIONER wanted to join well-established practitioner. New clinic building—90 miles east of St. Paul—city of 14,000. Early partnership with full hospital facilities. Ideal location. L. W. Picotte, M.D., Chippewa Falls, Wisconsin.

THE ADOLF GUNDERSEN MEDICAL FOUNDATION of La Crosse, Wisconsin, announces the establishment of a fully accredited three-year residency training program in Internal Medicine at Lutheran Hospital, La Crosse, Wisconsin. The hospital staff consists of a 65-man multiple specialty group with offices in a connecting modern clinic building. Eighteen fully qualified Internists serve as a nucleus of the teaching program. All staff men are full-time and salaried. This clinic-hospital complex serves as a referral center for a 100-mile radius. The hospital has a 375-bed facility. An intensive in-house training program is supported by weekly guest consultants. Stipend: $600 to $700 per month, plus housing and miscellaneous. Located in a progressive community with expanding university and private college. Population 50,000. Excellent school and recreation facilities. Applications being considered at all levels. Write: Edwin L. Overholt, M.D., Director, Medical Education and Research, Gundersen Clinic, Ltd., 1836 South Avenue, La Crosse, Wisconsin 54601.

GENERAL PRACTICE: INSTITUTIONAL: Desire a more regular life with regular hours, vacations, sick leave, time for attendance at meetings, etc? Consider working on a 60-bed medical service in a 350-bed psychiatric teaching hospital with a full-time Internist, several psychiatrists, part time surgeons and generalists at the Mental Health Institute, Cherokee, Iowa. Iowa licensure. Salary to $24,600 if eligible. Contact J. T. May, M.D., Superintendent.

INTERNIST—BROAD ELIGIBLE or Certified wanted to join two Internists, Radiologist, General Surgeon and EENT physician (all Mayo trained and Certified). Modern clinic building located in University city of Northeast Wisconsin having three fully equipped hospitals. For further information contact Administrator, Green Bay Clinic, 123 N. Military Ave., Green Bay, Wis. 54303.

WANTED: General Practitioner to join busy G. P. in ideal location. Partnership or salary with full hospital facilities. Contact M. J. Lindahl, M.D., Sherburn, Minnesota. Phone 507-764-4211 collect.

NEW EXPANDING OPPORTUNITIES for family physicians and physicians specializing in pediatrics, general surgery, internal medicine, urology, radiology, anaesthesiology; in medically-awakening community. Contemporary, automated, 105-bed, new hospital to be completed in the fall of 1970. Present hospital to be converted into long-term unit. Patient service area 50,000 people. Medical staff leading and supporting recruitment efforts. Excellent community location, forty miles equidistant to Milwaukee or Madison. Complete educational, cultural and recreational facilities. Possibility of new medical office building adjacent to new hospital. Immediate satisfaction in practice, income and family living. Special assistance if needed. Write or call Leo C. Bargielski, Administrator, Watertown Memorial Hospital, 1301 E. Main Street, Watertown, Wisconsin, 53094; telephone 414-261-4210 for more information.

OPPORTUNITY for career in occupational medicine with large corporation. Multiple locations. Salary plus fringes. Immediate openings in three locations. Give résumé. Write MINNESOTA MEDICINE—432, 375 Jackson, St. Paul 55101.

HALLOCK, MINNESOTA needs another general practitioner to help serve area population of 10,000. County seat town located in rich Red River Valley 65 miles north of Grand Forks or 65 miles south of Winnipeg. There is a facility in town, fully staffed and operating. Present solo general practitioner agreeable to employing, associating with, or cooperating with any practitioner interested. If interested, contact Roland Lartner, M.D. 843-4131.

WANTED: General Practitioner or Internist, to join four man group in St. Paul. Partnership possible in one year. Dr. V. L. Sommerdorf, 1239 Payne Avenue, St. Paul, Minnesota 55101.

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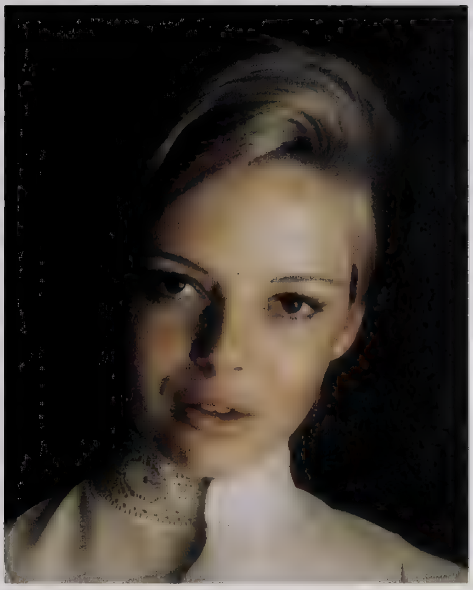
Fate can nothing better send than a true and loyal friend.—Julius Steger.



If she asks what you think of babyScott

The next page will help you answer.

Introducing the babyScott diaper system. Designed with infants, mothers, and physicians in mind.

Two-part system offers clinical advantages as well as convenience and efficiency.

The diaper panty: it takes anatomy into consideration. The babyScott diaper panty is specifically designed to hold the babyScott disposable diaper securely, yet without constriction. The panty fits low in front to avoid pressure on the umbilicus. And high on the legs so it won't chafe, bind or interfere with mobility.

Four different sizes and multi-position snaps help assure good fit and comfort. "Safety" pins, which can always pose a threat, are completely unnecessary.

All portions of the panty that come in contact with the infant's skin are covered with soft, quick-drying cloth.

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With babyScott, each diaper comes fresh and clean out of the pack. It's used only once, then flushed away or otherwis disposed of.

No soap, detergent or bleach residues. No opportunity for cross contamination from the diaper.

A frequently changed infant is a healthier, happier infant.
And the babyScott diaper system is so easy to use, it will be used.

babyScott®
the pinless diaper

Another fine quality product from Scott Paper Company

Dermatology

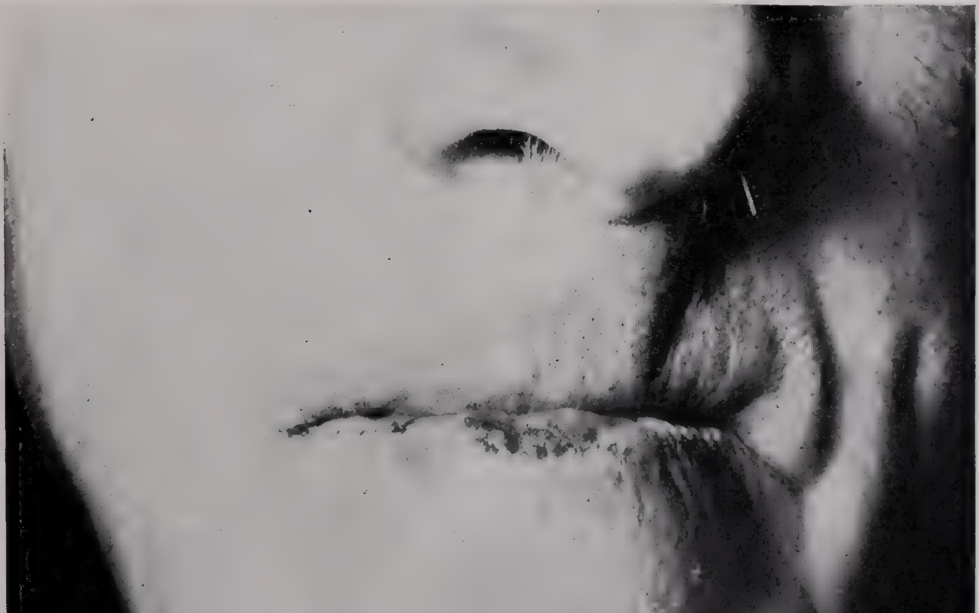
Leukoplakia

A Precancerous Dermatosis

THE TERM "precancerous" includes dermatoses in which the incidence of carcinoma is greater than should be expected when various factors such as age, exposure to sunlight, chronic irritation, and effects of previous treatments are considered. Leukoplakia, Bowen's disease, senile keratosis, cutaneous horn, and keratosis resulting from the ingestion of arsenic, exposure to tar, and iodizing radiation are precancerous. In at least 20% of these disorders squamous-cell carcinoma eventually develops. Seborrheic keratoses, certain nevi, tuberculous and stasic ulcers, lupus vulgaris, lupus erythematosus, epidermal cysts, and scars following burns are not precancerous. The incidence of carcinoma varies from only a fraction of 1% to about 5% in these disorders. Proper use of the term precancerous has a clinical and histologic meaning. It is valuable from the standpoint of prognosis and treatment.

Characteristics

Leukoplakia, derived from the Greek, means white plaque. Leukokeratosis implies that the lesion is thick and elevated. Leukoplakia occurs on the inner surfaces of the lips and cheeks, the dorsum and edges of the tongue, palate



Figure—Squamous-cell carcinoma superimposed on a leukoplakic area.

and gingivas. The disorder is not confined to the oral cavity; lesions may be present on the male and female external genitalia and the mucous membranes of the bladder, urethra, vagina, larynx, and esophagus.

The patches are usually white or grayish-white, superficial, and of various sizes and shapes. They may coalesce to form diffuse sheets distributed asymmetrically. An area becomes involved, peripheral extension follows, then other discrete plaques develop. The surface is glistening and opalescent, often reticulated, and the white pellicle is adherent to the underlying mucosa. Attempts to remove it forciby cause bleeding. Sometimes the lesions become elevated (leukokeratosis) and the surface irritated, inflamed, fissured, eroded, or ulcerated. These are "danger signals." The incidence of carcinomatous change in leukoplakia is difficult to determine: probably from 20 to 30%.

Clinical

Leukoplakia results from chronic irritation and trauma such as smoking, jagged or carious teeth, and poorly fitting dentures. Syphilis is unimportant. Leukoplakia appears most frequently during the fifth and sixth decades of life—occasionally during the second. The disease is much more common in men. Women who have the disorder are usually heavy smokers or have ill-fitting dentures.

Lichen Planus

Of all the maladies involving the oral cavity resembling leukoplakia, lichen planus* deserves first consideration. It may involve the buccal mucosa, the tongue, the lips, the hard palate, or the gingivas. Lesions are white, smooth papules with an inflammatory halo. They are annular, linear, or reticulated; they are rarely eroded. Lesions of lichen planus are not as thick as those of leukoplakia. The skin of the entire body should be examined carefully. Lichen planus frequently occurs on the flexor surfaces of the wrists and on the lower extremities.

Treatment

Treatment of leukoplakia consists of the removal of the local irritants, proper adjustment of dentures, cessation of smoking, and proper care of the teeth. Verrucous, fissured, or ulcerated lesions should be cauterized or desiccated. They are radioresistant. Surgical removal is occasionally indicated when the lesions are extensive.

Carl W. Laymon, M.D.†
Minneapolis, Minnesota

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*See Test Your Word Score Page 1761.

†Department of Dermatology, Hennepin County General Hospital, and the University of Minnesota Medical School, Minneapolis.

Reprint requests to 538 Southdale Medical Building, Minneapolis, Minnesota 55435.

Drink

Epitaph on an early Egyptian tomb: "His earthly tenement was shattered by wine, and his spirit departed before it was called for."—Telescope-Messenger

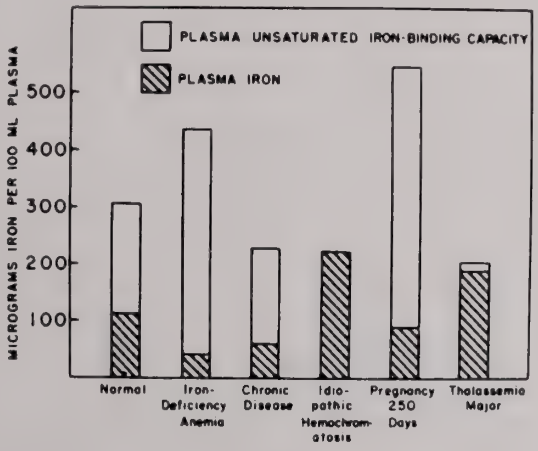
Laboratory Letter

Rusty About Iron Metabolism?

IF YOU FEEL inadequate about your knowledge of iron metabolism, don't. Even authorities are uncertain what happens once iron molecules enter the body—how and where they are absorbed, how they are transferred from mucosal cells to the plasma, what precise functions they perform, where they are stored, or why, in certain diseases, the body becomes overloaded with or depleted of iron molecules.

But for clinical purposes, you usually don't need to chase down metabolic pathways. Given a good history, physical, and the values for total iron and iron-binding capacity, you can reach some sound conclusions about the nature of your patient's problem.

To do so, you have to judge the significance and the relation of the plasma iron and iron-binding capacity. Do the values indicate iron-deficiency anemia, pyridoxine-responsive anemia, chronic disease, thalassemia major, or hemochromatosis? This is not always an easy question to answer. But as a practical matter, you will find the following figure (from Moore[1]) useful in separating these conditions.



Figure

Of course, in using the figure, you should take into acount these normal values: 50-180 micrograms per 100 ml for total iron and 250-400 micrograms per 100 ml for iron-binding capacity. It would be foolhardy to suggest this approach will completely unravel the problem of interpreting serum iron values. It will not. For example, if your patient has a hypochromic anemia (and that, after all, is the usual reason you order the tests), you will want to distinguish these types of anemias.

TABLE*

Type of Anemia	Diagnostic Criteria			
	Wright's Stained Blood Film	Bone Marrow Hemosiderin	Serum Iron	Miscellaneous Features
Iron deficiency	Hypochromia Microcytosis Few target cells	Absent or greatly reduced	Low	Evidence of blood loss; rarely malabsorption or deficient intake. Responds to iron therapy.
Thalassemia syndromes	Hypochromia Microcytosis Many target cells Nucleated Rbc Basophilic stippling	Increased or normal	Elevated or normal	Often Mediterranean ancestry; hepatosplenomegaly. Elevated fetal or A_2 Hgb; elevated bilirubin and other evidence of hemolysis.
Pyridoxine-responsive anemia	Hypochromia Microcytosis	Increased	Elevated	Rare; often abnormal tryptophane-loading test; responds to parenteral pyridoxine.
Hereditary hypochromic anemias	Hypochromia Microcytosis	Increased	Elevated	Type described by Cooley, Falls and Rundles occurs in males only; sideroachrestic type (Heilmeyer's) occurs mainly in males with sideroblasts in the bone marrow. Neither type responds to iron therapy.

*From Handbook of Clinical Laboratory Data.[2]

Richard L. Reece, M.D.
Minneapolis, Minnesota

References

1. Moore, C. V.: Iron Metabolism and Nutrition, The Harvey Lectures, Series 55, Academic Press, New York 1961.
2. Handbook of Clinical Laboratory Data, Second Edition, Edited by W. R. Faulkner, J. W. King, and H. C. Damm, The Chemical Rubber Co., Cleveland, Ohio, 1968.

Changes in the Spectrum of Disease

Variations in the spectrum of disease which doctors are called upon to treat have always been a reality in medicine, although in the recent past, the changes in the patterns of illness have been far more rapid and extensive than anything ever seen before. Recently, a young graduate of our medical school left practice in a small Minnesota town to become part of a missionary medical group in a medically backward country in Southeast Asia. In leaving, he announced that he expected to see "more real pathology" in two weeks in Asia than he would see in his Minnesota practice in a year. From the balance of his remarks, it seemed evident that he was going off to find a "real medical practice," suggesting that practice as it now exists in Minnesota has so changed from the established pattern as to no longer be the genuine article. The changing pattern of illness from the dramatic epidemic scourges of yesteryear to the heavy predominance of the deterioration of age, malignancy, etc., has obviously affected medical practice, although not always necessarily in obvious ways.*

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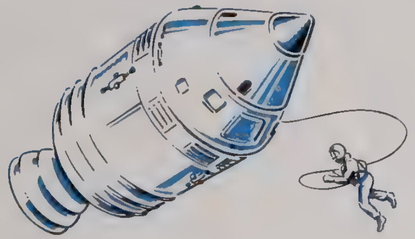
*Magraw, Richard M., M.D.: Ferment in Medicine, 1966.



Man in space, now fait accompli, re-emphasizes the importance of Uro-Phosphate therapy. Research into the effect of space travel on the astronaut reveals that weightlessness causes loss of bone calcium. As the bones are required to bear less and less of the weight of the body they lose calcium, increasing the calcium content of the urine. When physical activity is reduced, the acidity of the urine should be adjusted to keep increased calcium in solution . . . . a prophylaxis to prevent kidney or bladder calculi.

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2 tablets on retiring will keep residual urine acid and sterile, contributing to comfort and rest.

A clinical supply will be sent to physicians and hospitals on request.

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Side Effects: Gastrointestinal—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. *Skin*—maculopapular and erythematous rashes; exfoliative dermatitis; photosensitivity; onycholysis, nail discoloration. *Kidney*—dose-related rise in BUN. *Hypersensitivity reactions*—urticaria, angioneurotic edema, anaphylaxis. *Intracranial*—bulging fontanels in young infants. *Teeth*—yellow-brown staining; enamel hypoplasia. *Blood*—anemia, thrombocytopenic purpura, neutropenia, eosinophilia. *Liver*—cholestasis at high dosage.

Upon adverse reaction, stop medication and treat appropriately.

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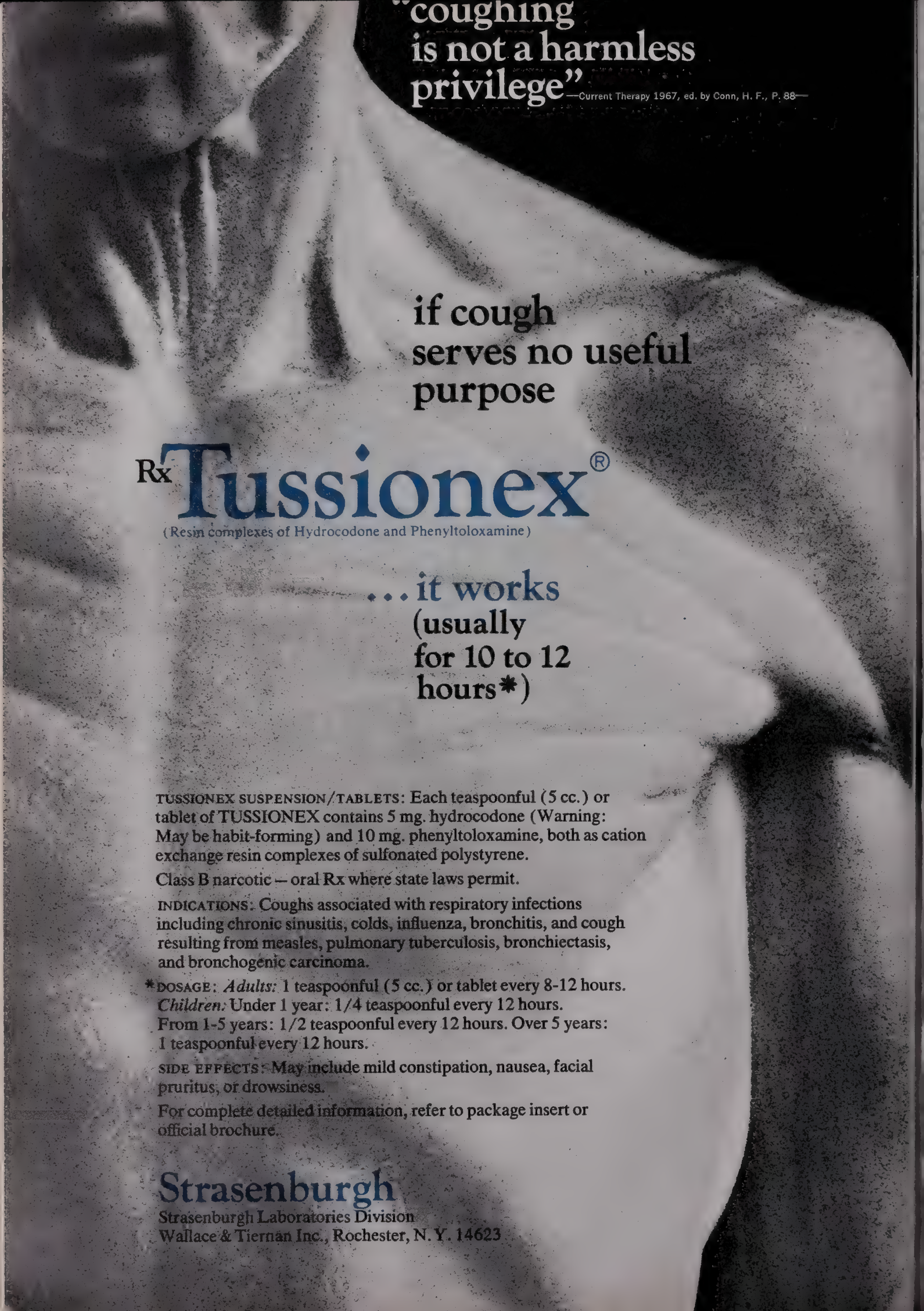

"coughing
is not a harmless
privilege"—Current Therapy 1967, ed. by Conn, H. F., P. 88—

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serves no useful
purpose

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for 10 to 12
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INDICATIONS: Coughs associated with respiratory infections including chronic sinusitis, colds, influenza, bronchitis, and cough resulting from measles, pulmonary tuberculosis, bronchiectasis, and bronchogenic carcinoma.

***DOSAGE**: *Adults:* 1 teaspoonful (5 cc.) or tablet every 8-12 hours. *Children:* Under 1 year: 1/4 teaspoonful every 12 hours. From 1-5 years: 1/2 teaspoonful every 12 hours. Over 5 years: 1 teaspoonful every 12 hours.

SIDE EFFECTS: May include mild constipation, nausea, facial pruritus, or drowsiness.

For complete detailed information, refer to package insert or official brochure.

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Grand Rounds

Penicillin Hypersensitivity*

MARY G. MAHERAS, M.D.
Minneapolis, Minnesota

An Immunological Approach

PENICILLIN IS considered non-toxic in man in spite of irritative effects; but, on the other hand, it is regarded as the most common cause of drug allergy. About 15% of the population is estimated to be sensitized.[1] Estimates of incidence vary from 1% to 10% of persons treated with penicillin; the lower figure may be more accurate in reference to an ambulatory population, while the higher figure may be more applicable to a hospital population.[2] In a recent study at Johns Hopkins University Hospital, 7.8% of hospitalized medical patients treated with penicillin had penicillin reactions.[3]

Diagnosis

The diagnosis of penicillin hypersensitivity may be very difficult to establish and is dependent on satisfying criteria of history, clinical findings, and proof of specific hypersensitivity.[4]

The History

Factors of historical significance include: atopy; family history of penicillin sensitivity; history of reaction to other drugs; frequency of penicillin exposure; route of penicillin administration; and type of penicillin preparation. Atopy, a positive family history, and other drug sensitivities are all associated with an increased incidence of penicillin hypersensitivity.[3,4]

The Preparation

There is also an increased rate of reaction with increasing frequency of exposure; the constant exposure to penicillin-contaminated products in the daily environment, such as milk products, may assume clinical significance.

---

*Presented as a Medical Grand Rounds at Hennepin County General Hospital, November 5, 1968.

Parenteral penicillin preparations are associated with higher incidences of sensitivity than oral or topical preparations.[1,4] Procaine preparations have an incidence of reaction of about 5%; aqueous preparations, about 2.5%; and oral and benzathine preparations, approximately 0.3%.[1]

Clinical Manifestations

The clinical manifestations of penicillin hypersensitivity are entirely nonspecific. Studies are cited in which maculopapular rashes, arthralgias, pruritus, and fevers occurred with equal frequency when healthy subjects were treated with either benzathine penicillin or saline. This was not true, however, in instances of serum sickness, urticaria, and local reactions; these clinical findings occurred more frequently in subjects treated with the benzathine penicillin.[3] Cutaneous reactions range from erythema and urticaria to syndromes of the Henoch-Schoenlein variety and lupus erythematosus. These reactions are usually only one manifestation of a generalized hypersensitivity state.[4]

Classification

The following classification of Levine will be used throughout the remainder of this paper when referring to the manifestations of penicillin sensitivity:[5]

Immediate Reaction (developing within two to 20 minutes)

1. Hypotension-shock
2. Diffuse urticaria
3. Wheezing
4. Rhinitis
5. Laryngeal edema

Accelerated Reaction (developing within two to 48 hours after the initiation of treatment)

1. Urticaria
2. Occasionally laryngeal edema

Late Reactions (developing after three days of treatment)

1. Skin rashes
2. Drug fever
3. Hemolytic anemia
4. Thrombocytopenia
5. Proteinuria with or without azotemia
6. Urticaria
7. Recurrent urticaria and arthralgia

Immunological Basis of Hypersensitivity:

Antigenicity of Benzylpenicillin:

$$\text{Antigen—Antibody} \longrightarrow \text{Allergic Reaction}$$

The first requirement for the induction of an immune response is a complete antigen. Studies have shown that low molecular weight compounds, such as penicillin, must react irreversibly with proteins to sensitize or elicit an allergic reaction. Penicillin itself has not been shown to combine irreversibly with protein; therefore it is postulated that either a contaminant or metabolic product must be the "pro-antigen," i.e., hapten, the substance that reacts irreversibly with tissue protein to form a complete antigen.[5,6] The irreversible binding of the hapten to the tissue protein is a chemical covalent bond. To form these bonds a portion of the drug molecule must be in a reactive form; the reaction occurs with amino acid residues such as lysine, tyrosine, or histidine, capable of forming a charge on their side chains.[6,7]

Levine and Ovary investigated the in-vitro reactions of benzylpenicillenic acid with various proteins (human gamma globulin, human serum albumin, gelatin, polylysine,) and found that benzylpenicillenic acid reacted primarily with lysine-E-amino groups to form a diastereomeric mixture of benzylpenicilloyl-lysine groups. A smaller reactivity occurred with disulfide linkages to form benzylpenicillenic acid cysteine-mixed disulfide, and D-penicillamine cysteine-mixed disulfide. By challenging rabbits sensitized with penicillin G they observed reactions specific for the benzylpenicilloyl-lysine groups. No antibodies to the the benzylpenicillenic acid-disulfide or D-penicillamine groups were detected. Using additional methods of precipitation, guinea-pig passive cutaneous anaphylaxis, and quantitative inhibition with E-amino caproic acid they further confirmed the specificity for the diastereomeric benzylpenicilloyl groups. They thus concluded that benzylpenicilloyl-lysine groups are major antigenic determinants for penicillin G hypersensitivity, and that the penicillin system behaves similarly to protein and protein-conjugated systems with precipitating antibodies, skin-sensitizing antibodies, and hapten inhibition.

The failure of the mixed disulfide conjugates to form detectable antibodies was attributed to insufficient formation of conjugates containing these groups in vivo, and therefore insufficient antibody formation. Serum albumin and globulin contain many lysine-E-amino groups, but relatively very few disulfide linkages; conversely, epidermal proteins contain relatively large numbers of cysteine disulfide linkages.

Parker et al. subsequently investigated the benzylpenicilloyl and benzylpenicillenate groups as specific determinants of allergic benzylpenicillin reactions in humans. They employed the method of eliciting wheal and erythema responses, and univalent hapten inhibition. They concluded that multifunctional derivatives of penicillenic acid are effective elicitors of wheal and erythema responses in humans allergic to penicillin. Significant derivatives are penicilloyl, penicillenate, and penamaldate-penilloaldehydes. The former is the major determinant, and the latter two minor determinants.[9] Some 95% of penicillin that is bound is in the form of the benzylpenicilloyl group.[5]

Parker's study is summarized in the following table:[9]

TABLE I

History	BPO-Lys skin test		Penicillenate-S-HSA skin test			
	+	—	+BPO test		—BPO test	
			+	—	+	—
Previous allergic reaction	45	14	12	10	0	6
No previous allergic reaction	44	1147	12	12	0	12

Out of the total 1250 subjects tested only two had systemic reactions to the skin test; both of these tests included the penicillenate-S-HSA. The use of BPO polylysine derivatives themselves has not been found to elicit detectable antibody formation.

Antibody Formation

The immunoglobulins, i.e., antibody-carrying globulins, are the gamma and beta globulins. These globulins are composed of light and heavy polypeptide chains and are divided into four major classes according to the heavy (H) chains:

IgG
IgM
IgA
IgD

As shown from animal studies, different antibody classes mediate different allergic reactions. For example, there is some data to indicate that immunoglobulin G and immunoglobulin M antibodies fix complement and therefore mediate serum sickness and hemolytic reactions. Investigators have not yet been able to classify skin-sensitizing antibodies; functionally, however, we do know that these antibodies are specific for the immunizing antigenic determinant.

Only semi-quantitative methods are available currently for antibody assays. The wheal and flare reaction is used for the detection of skin-sensitizing antibodies (SSA), i.e., antibodies that are fixed to the skin. The benzylpenicilloyl skin-sensitizing antibodies are detected with the low molecular weight benzylpenicilloylpolylysine conjugates. The reaction is elicited by bridging a small number of "tissue-fixed" skin-sensitizing antibody molecules, which results in histamine release. The skin-sensitizing antibody of the minor antigenic determinants is detected by testing with a minor determinant mixture of benzylpenicillin, benzylpenicilloate, and benzylpenilloate; these determinants probably react with protein in the skin to form the complete antigen that can react in the wheal and flare.

Benzylpenicilloyl specific immunoglobulin G and immunoglobulin M antibodies can be determined by hemagglutination methods employing OS human red blood cells that have coupled to benzylpenicilloyl groups. To date no method for assaying immunoglobulin G or immunoglobulin M antibodies specific for the minor determinants has been developed.[5]

Inferences from Table 2 and other data can be applied to the classification of allergic penicillin reactions presented previously.

Immediate Reactions

These reactions are nearly 100% associated with minor determinant skin-sensitizing antibodies. Prospective studies have shown that persons with positive wheal and flare reactions to the minor determinants have immediate reactions when challenged with penicillin. Persons with immunoglobulin G or immunoglobulin M antibodies only have failed to develop the immediate reaction.

Accelerated Reactions

The accelerated hypersensitivity reactions have been associated with skin-sensitizing antibodies and immunoglobulin G antibodies of penicilloyl specificity. It is postulated that they are mediated by skin-sensitizing antibodies and that the immunoglobulin G antibodies serve as "blocking" antibodies. A rising immunoglobulin G titer has been associated with the disappearance of urticarial reactions in spite of continued treatment with penicillin. Prospectively, patients developed their urticaria at low titers of immunoglobulin G, and it disappeared with the anamnestic response and rising titers. A negative set of skin tests can rule out the possibility of immediate or accelerated reactions.

Late Reactions

The late urticarial reactors also seem to be mediated by benzylpenicilloyl specific skin-sensitizing antibodies. Whereas the accelerated urticarial reactors already have a titer of antibodies when they are challenged, the late urticarial reactors develop their titer during the course of treatment; i.e., the course of treatment provides both the sensitizing and the challenging dose in the late urticarial reactors.

Of interest was the near 100% association of minor determinant skin-sensitizing antibodies with the late reaction of current urticaria and arthralgia. In contrast to the immediate reactions, which are apparently more sensitive to benzylpenicilloate, these reactors are more sensitive to benzylpenicillin.

Maculopapular and erythematous reactions were associated with high titers of immunoglobulin M antibodies; it is postulated that they may be mediated by double antigen-antibody reactions. An immunoglobulin titer of greater than 1:1000 adds support to a diagnosis of maculopapular penicillin sensitivity.

Some 5-10% of patients on long-term parenteral penicillin therapy may develop a Coombs' positive hemolytic anemia. The hemolytic reaction occurs when benzylpenicilloyl specific antibodies react with erythrocyte-benzylpenicilloyl conjugates. A high titer of immunoglobulin G antibodies may increase the incidence of hemolysis.[5]

TABLE 2

MECHANISMS OF ALLERGIC REACTIONS:

Antibody Patterns in Nonreactors to Benzylpenicillin[6]

	Percentage of patients with antibody pattern		
Antibody pattern	117 with no penicillin therapy	103 with recent moderate dose therapy	12 with recent high dose therapy
None detected	3	0	0
IgM only	77	61	92
IgG and IgM	17	30	8
SSA to BPO plus IgG and IgM	3	8	0
SSA to BPO plus SSA to minor determinants plus IgG and IgM	0	1	0

Nearly 100% of the non-reactors demonstrated the presence of antibodies. This data demonstrates that the presence of antibodies does not necessarily mean sensitivity. One must consider the type and quantity of antibody as well as individual differences.

Antibody Patterns in Allergic Reactors to Benzylpenicillin[6]

	Percentage of patients with antibody pattern:				
Antibody Pattern:	12 immediate reactions	10 accelerated reactions	11 late urticarial reactions	16 recurrent urticaria & arthralgia	15 maculopapular & erythema reactions
IgM only	0	0	0	0	58
IgM (high titers)	0	0	0	0	32
SSA to BPO plus IgG and IgM	0	60	91	0	5
Minor determinant SSA plus IgM	42	0	0	56	0
Minor determinant SSA plus IgM & IgG	16	0	0	25	0
BPO-SSA, minor determinant SSA, IgG, IgM	42	40	9	19	5

Clinical Detection of the Penicillin Reactor

A primary concern in clinical medicine is the detection of the potential anaphylactic reactor whenever the slightest possible history of penicillin allergy is encountered. Investigators have demonstrated the predictive value of skin testing and the relative safety of treating with penicillin in the presence of negative skin tests.[10,11] As pointed out by Levine, however, it is necessary to include the minor determinants in the skin-testing procedures; currently the necessary antigenic substances are not available for widespread clinical use. Clinicians are thus still required to use second choice antibiotics in situations where penicillin is regarded as the drug of choice.

Hemagglutinating techniques are available, but at this time they are highly impractical on a large scale and of very questionable validity as to predictive values.[12]

An in-vitro procedure based on the microscopic degranulation of basophils during the antigen-antibody reaction is also described. The degranulation of the basophils is representative of histamine release. A positive test means only that a measurable titer of antibodies was present at the time the test was carried out.[13,14] This procedure is also impractical, and involves considerable subjective human interpretation.

A more recent test based on the fluorometric assay of histamine released from rabbit basophils is under investigation. It is dependent on histamine release from rabbit basophils when the cells are mixed with sensitized sera and penicillin.[15] This test is more scientifically and technically controlled than the previously described degranulation test, but no clinical studies are available in the literature.

In summary, an outline is provided for an immunological understanding of the clinical entity of penicillin allergy. Its clinical application is limited because of the impracticality of large-scale efforts to determine potential reactors, the unavailability of laboratory techniques in the average hospital, and the availability of increasing numbers of effective substitute antibiotics.

It is left for the clinician to take such prophylactic measures as a thorough history, the use of penicillin only when indicated, the use of the minimal dosage necessary for the therapy, the use of the safest route possible, the use of the safest preparation indicated, and preparation for reactions.[4] It is hoped that advantage will be taken of whatever skin-testing procedures or laboratory techniques are available.

Clinical Case Report

The patient was an 18-year-old student nurse who was hospitalized at age 16 for a period of two weeks because of rheumatic fever. She was told by her physician that she had a heart murmur initially which disappeared during hospitalization. She was discharged on prophylactic penicillin and convalesced for a period of four months.

Ten days prior to the current admission she developed a sore throat and swollen cervical nodes. The initial throat culture taken in the Emergency Room was negative; but as repeat culture was positive for beta hemolytic streptococcus, she received intramuscular penicillin (bicillin). The day following the injection a rash resembling "insect bites" developed on her lower extremities. She was again seen in the Emergency Room and started on a course of Prostaphlin for suspected folliculitis. The following day she noted the onset of pain in the left ankle and left elbow and was admitted to the hospital.

Physical examination on admission was positive for small posterior cervical nodes, a low-grade systolic murmur in the pulmonic area, and a tender left ankle and left elbow; a macular rash was present on the trunk.

During her hospital course she remained afebrile and was free of the rash and arthralgia within 48 hours. Laboratory data revealed a persistent eosinophilia of 8-11% and an ASO titer that rose from 250 to 500. Her final diagnosis was that of penicillin allergy and she was discharged on prophylactic sulfadiazine.

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Erratum

There is one error in my editorial "Fifty Years Ago" which I missed—my fault. On page 1077 of the July issue of MINNESOTA MEDICINE last paragraph—Stipends in Child Psychiatry should read *Stipends in Pediatrics.*

Hyman S. Lippman, M.D.
St. Paul, Minnesota

The Progress Notes of Hypocrates

Meton* was seized with fever; there was a painful weight in the loins. Next day, after drinking water pretty copiously, had proper evacuations from the bowels. On the third, heaviness of the head, stools thin, bilious, and reddish. On the fourth, all the symptoms exacerbated; had twice a scanty trickling of blood from the right nostril; passed an uncomfortable night; alvine discharges like those on the third day; urine darkish, had a darkish cloud floating in it, of a scattered form, which did not subside. On the fifth, a copious hemorrhage of pure blood from the left nostril; he sweated, and had a crisis. After the fever restless, and had some delirium; urine thin, and darkish; had an affusion of warm water on the head; slept and recovered his senses. In this case there was no relapse, but there were frequent hemorrhages after the crisis.†

Editor's diagnosis and treatment: Hypertension-Kidney, Dietary Therapy. Your diagnosis and treatment?

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*Meton—a patient.
†Hippocrates.

Some people won't take it with them because they didn't save any to take.—Herbert Prochnow

Famous Men and Their Poor Health

"Good God! What a man! What a genius! Such knowledge and such a mind!" This was Gustave Flaubert's tribute to Baruch Spinoza whose all too short life spanned only the years between 1632 and 1677.

In Hebrew Baruch means blessed. And young Spinoza was blessed—mentally, morally, spiritually—but not physically. As a tubercular child refugee from the Spanish Inquisition he accompanied his family to Holland where he grew up in Amsterdam Jewry but spent most of his adult life in the little Dutch town of Voorburg. There we see him living alone in a small, dusty room industriously grinding and polishing lenses for a meager subsistence.

Why the vocation of lens-grinder and polisher? The good Jew of Spinoza's era conscientiously honored and observed the traditional admonition that to be whole a man should learn and engage in a solid and worthy handicraft. "He who earns his living by toil is greater than he who fears God," said the Talmud. And it so happened that scientifically-oriented Baruch was attracted to lens-craft for three reasons in particular: from reading Descartes he had become interested in the field of optics; Huygens' telescope had recently discovered Saturn's largest satellite; and Leeuwenhoek was just then engaged in refining and perfecting the microscope that would later furnish a detailed view of blood corpuscles. Then too, while grinding and polishing, Baruch could think: formulate his majestic philosophical concepts and plan his literary work.

Considering his inexorably advancing phthisis, however, he could scarcely have chosen a more deleterious occupation. Dust filled his closed, cramped room and was inhaled into his diseased lungs. But, perfectionist that he was, he continued with each lens until it reached the acme of perfection. In Robert Smith's book on optics he says that for mere adequacy a single lens requires as many as 3,000 strokes on each side. And Baruch used only a treadle lathe!

He didn't go out for fresh air. Milk porridge and groats comprised his scanty diet. "Nature is satisfied with very little, and if nature is satisfied then so am I," he said.

So, emaciated, flushed, coughing, sweating, spitting, often too weak to stand without support, young Spinoza ineluctably wasted away. If he wondered why, he never asked or complained. But as the mortal body faded to a mere shadow, the inner spiritual light glowed the brighter in its transcendence of the corporeal and the temporal. Transfiguration, we call the phenomenon!

One Sunday morning Baruch had his usual cheerful chat with his landlady's family, agreeing to continue the conversation after their return from church. But the visit was never resumed. Baruch went to bed, his doctor sitting at his side, and quietly died. That is, his body did. But not his spirit. For it, resurrection followed in the posthumous publication of his philosophical and literary masterpiece (15 years in the writing and prudently withheld during his lifetime): his "Ethics," whereby he bequeathed to the ages his magnificent philosophical tenets: that mind and matter are not a dichotomy but twin attributes of Reality; that man is not a special creation but rather a single aspect of the vast immanence of Nature (God) as revealed in the total cosmos.*

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*With quotations from and acknowledgments to Rudolf Kayser: Spinoza, 1946.

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Medicine in History

Childhood Rickets:

Revival of an Ancient Menace

When has any physician last seen a child with rickets? Readers of the JAMA[1] may have been surprised recently by the report of an outbreak in Canada of childhood rickets of near epidemic proportions. Dr. Charles R. Scriver has stated that each year about 50 children with rickets have been admitted to Montreal Children's Hospital. In Quebec, the disease rate is 10 times higher than in the United States. A recent survey of 226 institutions in the United States showed that the incidence of rickets was only one child per 2,791 admissions.

What then accounts for this difference? In Canada, there is no compulsory legislation to force the provinces to comply with the 1965 recommendations of the Canadian Federal Government that milk should contain 300 to 400 international units of vitamin D per quart. Dr. Gelinas, the Quebec Deputy Minister of Health, is presently working with various medical, federal, and provincial groups in an effort to formulate and pass mandatory legislation.

A Brief History of the Clinical Investigation of Rickets

Findlay[2] stated that the first reference to rickets can be attributed to Soranus of Ephesus (98-138 A.D.), who claimed that the disease occurred in children because of the neglect of the Roman mothers and the cold and dampness of the domiciles. In 1650 Glisson[3] presented the first definitive clinical and pathomorphologic work of any scientific significance. Previously, in 1645, Whistler[4] had discussed rickets in his work "De Morbo Puerili Anglorum." No doubt the title was responsible for the appellation "English disease" being given to rickets by German and other European writers. The term persisted even until the latter part of the 19th century, as witnessed in Kisel's[5] report in 1897 of English disease in the children of Moscow.

In 1895 Snow[6] conducted an extensive investigation of environmental factors as a cause of rickets in the children of Italian immigrants living in Buffalo, N. Y. Snow noted that the incidence of childhood rickets in Italy was low, whereas the incidence in the immigrant children was very high. He concluded that lack of housing, inadequate sunshine, improper food, and frequent childhood maladies combined to produce a high incidence of childhood rickets. Such thinking persisted in American pediatrics for an additional 25 years.

The Recognition of the Efficacy of Cod Liver Oil

According to Park,[7] Trousseau and his student, Bretonneau, two French physicians of the 18th century, advocated cod liver oil as a specific remedy in the therapy of rickets.

In 1878, Cheadle[8] presented the case histories of three children who had scurvy and rickets, but cod liver oil was given to only one of the three, affirming that Cheadle had neither the knowledge nor the conviction as to the specificity of cod liver oil in the therapy of rickets.

In 1909 Schabad,[9] a Russian pediatrician, demonstrated in studies of metabolic balance in children with rickets that administration of cod liver oil and phosphorus was associated with increased retention of calcium and phosphorus when the group was compared to rachitic children who were untreated. In England in 1919 Mellanby[10] isolated an organic fat-soluble substance that effectively prevented experimental rickets in puppies. In 1924 Windaus[11] isolated crystalline vitamin D by irradiation of ergosterol.

In the United States, Shipley and associates[12] in 1921 demonstrated proof of the curative action of cod liver oil by the deposition of lime salts in the cartilage of rachitic rats.

Even at the present time, the essential action of vitamin D remains unknown, though the transport of calcium and phosphate ions is somehow influenced thereby, and vitamin D is important in the regulation of the concentration of these ions at three loci—intestines, kidney, and bone.

In the 1950s, the possibility that the addition of vitamin D to milk could be excessive was proved. This excess resulted in many instances of hypercalcemia in Great Britain as well as in the United States. Also noted was the association of supravalvular aortic stenosis in these children with hypercalcemia. Subsequently, such lesions have been produced in puppies through excessive dosage of vitamin D to pregnant bitches.

Geographic Distribution of Rickets

Rickets is a disease that predominates in the temperate zones. It had been recognized that rickets was more prevalent in industrial areas because of poor housing and diminished sunlight exposure. By contrast, the disease was almost nonexistent in coastal areas of the same temperate zones because of the prevalence of fish in the diet. Herring and mackerel, common foods in these coastal areas, have a high content of vitamin D, namely 1,500 units of vitamin D per 100 gm. Eskimos have a diet consisting principally of fish and animal oils, a fact that has prevented rickets in their children.

Rickets Today

Three stages in the development of childhood rickets are recognized. Hypocalcemia and tetany in infants represent the first stage. The second stage, occurring at five to seven months of age, is manifested by normal levels of serum calcium but low levels of serum phosphorus and by hyperaminoaciduria. In the third stage, clinical rickets is evident radiologically as well as clinically.

Recognition of low serum calcium and phosphorus values and the use of a urine screening test for hyperaminoaciduria are important in children suspected of having latent or incipient rickets. Basically, rickets is a disease of poverty, and the opportunities provided by the Head Start Program may serve as an important means of checking on the nutrition of young children from ghetto and underprivileged areas. While we have been busy with contemporary problems of communicable diseases and vaccines, childhood rickets, an age-old scourge of the health of children, has returned.

Edmund C. Burke, M.D.*
Rochester, Minnesota

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*Mayo Clinic and Mayo Foundation: Section of Pediatrics.

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Exorcism*

"I exorcise thee, Peter, or thee, Barbara, being weak but reborn in Holy Baptism, by the living God, by the true God, by God Who redeemed thee with His precious Blood, that thou mayest be exorcised, that all the illusions and wickedness of the devil's deceits may depart and flee from thee together with every unclean spirit, adjured by Him Who will come to judge both the quick and the dead, and who will purge the earth with fire. Amen."

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*Prayer of exorcism for persons possessed of the devil from "Malleus Maleficorum". Heinrich Kramer and James Sprenger. Published ca 1486. English translation by Montague Summers. Pushkin Press. London. 1928.

IT'S THE LAW

No Negligence in Treatment of Perirectal Wound

The patient received a perirectal wound while water skiing. His physician observed the wound and cleaned it. He did not suture it. While the patient was still in the physician's office, the wound began bleeding. The physician once again examined the wound and sutured it. He placed the patient in the hospital for observation. The following day the patient was released from the hospital and returned to his home in a neighboring city.

Subsequently, he required hospitalization and a laparotomy for removal of a contaminated jagged wood splinter within the peritoneal cavity which had caused peritonitis, infection and putrefaction. Malpractice suit was brought against the initial examining physician. The court held, however, that the initial examining physician was not in error in his treatment of the wound.

The Citation. 19:8, August 1, 1969. McClellan v. French, 439 S.W.2d 813 (Ark., April 21, 1969).

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INDICATIONS: Patients with moderate to severe anxiety and/or agitation and depressed mood; patients with depression in whom anxiety and/or agitation are severe; patients with depression and anxiety in association with chronic physical disease; schizophrenics with associated depressive symptoms.

CONTRAINDICATIONS: Central nervous system depression from drugs (barbiturates, alcohol, narcotics, analgesics, antihistamines); bone marrow depression; urinary retention; pregnancy; glaucoma. Do not give in combination with MAOI drugs because of possible potentiation that may even cause death. Allow at least 2 weeks between therapies. In such patients therapy with TRIAVIL should be initiated cautiously, with gradual increase in the dosage required to obtain a satisfactory response.

WARNINGS: Patients should be warned against driving a car or operating machinery or apparatus requiring alert attention, and that response to alcohol may be potentiated.

PRECAUTIONS: Suicide is always a possibility in mental depression and may remain until significant remission occurs. Supervise patients closely in case they may require hospitalization or concomitant electroshock therapy. Untoward reactions have been reported after the combined use of antidepressant agents having various modes of activity. Accordingly, consider possibility of potentiation in combined use of antidepressants. Not recommended for use in children. Mania or hypomania may be precipitated in manic-depressives (perphenazine in TRIAVIL seems to reduce likelihood of this effect). If hypotension develops, epinephrine should not be employed,as its action is blocked and partially reversed by perphenazine. Caution patients about errors of judgment due to change in mood.

SIDE EFFECTS: Similar to those reported with either constituent alone.

Perphenazine: Should not be used indiscriminately. Use caution in patients with history of convulsive disorders or severe reactions to other phenothiazines. Likelihood of untoward actions greater with high doses. Closely supervise with any dosage. Side effects may be any of those reported with phenothiazine drugs: blood dyscrasias (pancytopenia, thrombocytopenic purpura, leukopenia, agranulocytosis, eosinophilia); liver damage (jaundice, biliary stasis); extrapyramidal symptoms (opisthotonos, oculogyric crisis, hyperreflexia, dystonia, akathisia, dyskinesia, parkinsonism) usually controlled by the concomitant use of effective antiparkinsonian drugs and/or by reduction in dosage, but sometimes persist after discontinuation of the phenothiazine; severe acute hypotension (of particular concern in patients with mitral insufficiency or pheochromocytoma); skin disorders (photosensitivity, itching, erythema, urticaria, eczema, up to exfoliative dermatitis); other allergic reactions (asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions); peripheral edema; reversed epinephrine effect; endocrine disturbances (lactation, galactorrhea, disturbances of menstrual cycle); grand mal convulsions; cerebral edema; altered cerebrospinal fluid proteins; polyphagia; paradoxical excitement; photophobia; skin pigmentation; failure of ejaculation; EKG abnormalities (quinidine-like effect); reactivation of psychotic processes; catatonic-like states; autonomic reactions such as dryness of the mouth, headache, nausea, vomiting, constipation, obstipation, urinary frequency, blurred vision, nasal congestion, and a change in the pulse rate; hypnotic effects; pigmentary retinopathy; corneal and lenticular pigmentation; occasional lassitude; muscle weakness; mild insomnia; significant unexplained rise in body temperature may suggest intolerance to perphenazine, in which case discontinue. Antiemetic effect may obscure signs of toxicity due to overdosage of other drugs or make diagnosis of other disorders such as brain tumors or intestinal obstruction difficult. May potentiate central nervous system depressants (opiates, analgesics, antihistamines, barbiturates, alcohol), atropine, heat, and phosphorous insecticides.

Amitriptyline: Careful observation of all patients recommended. Side effects include drowsiness (may occur within the first few days of therapy); dizziness; nausea; excitement; hypotension; fainting; fine tremor; jitteriness; weakness; headache; heartburn; anorexia; increased perspiration; incoordination; allergic-type reactions manifested by skin rash, swelling of face and tongue, itching; numbness and tingling of limbs, including peripheral neuropathy; activation of latent schizophrenia (however, the perphenazine content may prevent this reaction in some cases); epileptiform seizures in chronic schizophrenics; temporary confusion, disturbed concentration, or transient visual hallucinations on high doses; evidence of anticholinergic activity, such as tachycardia, dryness of mouth, blurring of vision, urinary retention, constipation, paralytic ileus; agranulocytosis; jaundice. The antidepressant activity may be evident within 3 or 4 days or may take as long as 30 days to develop adequately, and lack of response sometimes occurs. Response to medication will vary according to severity as well as type of depression present. Elderly patients and adolescents can often be managed on lower dosage levels.

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Physician's Workshop

The Velcro Rale

A PHYSICAL SIGN with high specificity of meaning is of inestimable value to the clinician. Proper elicitation or identification of such a sign is, however, often fraught with difficulty. Among the most difficult signs to identify correctly and, moreover, to teach to students are those generated by sound. Sounds related to auscultation of the lungs, by and large, bear relatively nonspecific meaning to such an extent that some chest physicians consider the stethoscope to be an anachronistic tool. This view notwithstanding, it is my opinion that sounds generated by the lung can be extremely helpful to less skeptical clinicians.

It has long been recognized that "dry" or "crackling" rales have been associated with pulmonary fibrosis. These rales have been compared to the crackling of cellophane. In my experience these descriptions are not satisfactory in terms of teaching because of their vagueness and lack of reproducibility for demonstration. I have found that the sound generated by tearing apart mated strips of Velcro adhesive, often used as fasteners on blood pressure cuffs, represents a striking reproduction of the rales of pulmonary fibrosis. In addition, the sound is easy to demonstrate repetitively to students and rapidly and effectively fixes it in their memories. The sound seems specific for pulmonary fibrosis. I have not heard it in other diffuse pulmonary conditions such as sarcoidosis, lymphogenous metastatic carcinoma, or pulmonary congestion. I have found the presence of digital clubbing and so-called Velcro rales almost diagnostic of pulmonary fibrosis.

The next time a clinician removes his Velcro-equipped blood pressure cuff from a patient's arm, he is urged to take note of the sound.

Richard A. DeRemee, M.D.*
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Automation and Medicine

Most physicians tend to think of computers in medicine as having a "far out into the wild blue yonder" aspect. To some this is stimulating; however, many persons tend to resent things which are hard to understand and the normal reaction is one of conservatism . . . As understanding and experience improve, physicians can move from conservatism to active use of these splendid instruments in the practice of medicine.*

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*A. H. Schwichtenberg in Richard Magraw: Ferment in Medicine, 1966.

Minnesota Medicine Survey

Dear Doctors:

We are having financial budget problems in Minnesota Medicine, and it is mandatory for the moment that budgets be met. In order that we might know whether or not you think Minnesota Medicine should continue, it is imperative that you fill in the following questionnaire. Carl O. Rice, M.D.

1. I read Minnesota Medicine. None, 25, 50, 75, 100 percent.
2. I read the advertisements. None, 25, 50, 75, 100 percent.
3. To continue Minnesota Medicine I would be willing to allocate from my annual dues a subscription price of—None, $5, $10, $15, $20.
4. I read the following sections: None, 25, 50, 75, 100 percent of the time:

   Scientific____%; Editorials____%; Letters to the Editor____%; Editor's Soliloquy____%; Quotes at the bottom of articles____%; Full page fillers ____%; Viewing Box____%; CPC's____%; Curbstone Consultations ____%; Fracture Conferences____%; Tumor Conferences____%; Grand Rounds____%; Advances____%; Reviews____%; Physician's Workshop ____%; Special Articles____%; Meetings & Announcements____%; Lab Letters____%; Physician's Diary____%; Dermatology____%; Abstracts ____%; Test Your Word Score____%; Book Reviews____%; History of Medicine____%; In Memoriam____%; Minnesota Medicine at a Glance ____%.
5. My specialty is____________________ Resident____ Intern____ Medical Student____
6. I suggest____

   ____

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Your answers may determine whether or not Minnesota Medicine shall continue as our journal.

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When stress is situational—environmental pressure, worry over illness—the treatment often calls for an anxiety-allaying agent which has a prompt and predictable calming action and is remarkably well tolerated. BUTISOL SODIUM (sodium butabarbital) meets this therapeutic need.

After 30 years of clinical use . . . still a first choice among many physicians for dependability, safety and economy in mild to moderate anxiety.

Contraindications: Porphyria or sensitivity to barbiturates.

Precautions: Exercise caution in moderate to severe hepatic disease. Elderly or debilitated patients may react with marked excitement or depression.

Adverse Reactions: Drowsiness at daytime sedative dose levels, skin rashes, "hangover" and systemic disturbances are seldom seen.

Warning: May be habit forming.

Usual Adult Dosage: As a daytime sedative, 15 mg. (¼ gr.) to 30 mg. (½ gr.) t.i.d. or q.i.d.

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BUTICAPS® [Capsules BUTISOL SODIUM (sodium butabarbital)] 15 mg. (¼ gr.), 30 mg. (½ gr.).

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Fire victim. Examination reveals second degree burn of lower leg. To combat shock, restore circulatory volume and replace protein loss, plasma is administered. Local pressure dressing applied. Limb elevated to limit the flow of lymph. About 36 hours after admission the patient develops an elevated temperature and complains of pain at the site of the lesion. Dressing removed. A suppurating slough area has developed over part of the burn. A swab specimen is taken for culture and the slough area is debrided. Antibacterial treatment is begun with Terramycin I.M. Days later, recovery is progressing, and the laboratory report shows a mixed infection with a predominance of susceptible coliform bacteria, confirming the therapeutic choice. Terramycin therapy is continued until all signs of infection disappear.

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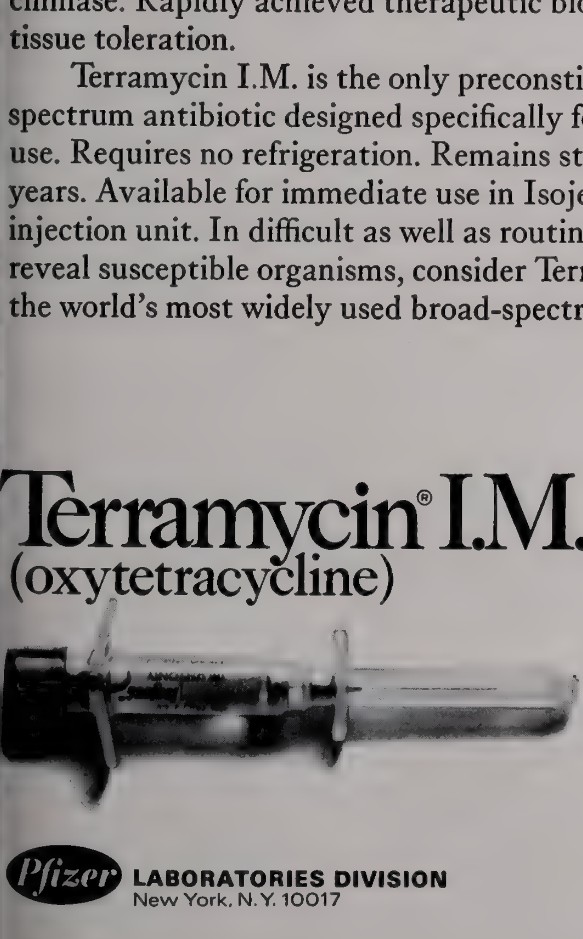

Pfizer LABORATORIES DIVISION
New York, N.Y. 10017

Contraindicated: In individuals hypersensitive to any of the components of this drug.

Warnings: If renal impairment exists, even usual doses may lead to excessive systemic accumulation and possible liver toxicity. In such patients, lower than usual doses are indicated and for prolonged therapy oxytetracycline serum level determinations may be advisable.

Terramycin may form a stable calcium complex in any bone-forming tissue with no serious harmful effects reported thus far in humans.

Use of oxytetracycline during the last trimester of pregnancy, neonatal period and early childhood may cause discoloration of teeth. This effect occurs mostly during long-term use of the drug, but it has also been observed in usual short-treatment courses.

During treatment with tetracyclines, individuals susceptible to photodynamic reactions should avoid direct sunlight. Discontinue therapy at first evidence of skin discomfort.

Note: With oxytetracycline, phototoxicity is not believed to occur and photoallergy is very rare.

Precautions: Use of broad-spectrum antibiotics occasionally may result in overgrowth of nonsusceptible organisms. Where such infections occur, discontinue oxytetracycline and institute specific therapy.

As with all intramuscular preparations, Terramycin Intramuscular Solution should be injected well within the body of a relatively large muscle. *Adults:* The preferred sites are the upper outer quadrant of the buttock (i.e., gluteus maximus), or the mid-lateral thigh. *Children:* It is recommended that intramuscular injections be given preferably in the mid-lateral muscles of the thigh. In infants and small children the periphery of the upper outer quadrant of the gluteal region should be used only when necessary, such as in burn patients, in order to minimize the possibility of damage to the sciatic nerve.

The deltoid area should be used only if well developed such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Increased intracranial pressure with bulging fontanelles has been observed occasionally in infants receiving therapeutic doses of the drug, but such signs and symptoms have disappeared rapidly on cessation of treatment with no sequelae.

Adverse Reactions: Subcutaneous and fat-layer injection may produce mild pain and induration which may be relieved by an ice pack. Very mild gastrointestinal disturbances, not requiring discontinuance of the drug, may occur occasionally. Allergic reactions, including anaphylaxis, rarely have been observed.

Dosage: *Adult:* The optimal dosage varies, depending on the type and severity of infection. Unless otherwise specified, a dose of 100 mg. every 8 to 12 hours, or a single daily dose of 250 mg. should be adequate for the treatment of most mild or moderately severe infections. In severe infections, 100 mg. every 6 to 8 hours, or 250 mg. every 12 hours may be necessary.

Serum levels obtained by the recommended dosages are comparable to those provided by the oral dosage of 1 to 2 Gm. daily in adults. Antibiotic therapy should be continued for at least 24 to 48 hours after all symptoms and fever have subsided.

In certain diseases specific courses of therapy may be recommended as a general guide. In primary and secondary syphilis for example, the daily administration of 2 Gm. oxytetracycline, orally, in divided doses for two weeks has given good results. In cases of gonococcal infection two intramuscular injections of 250 mg. each, or one intramuscular injection of 250 mg. combined with one gram given orally as a single dose, will usually suffice, but repetition of this therapy will be required in an occasional case.

In the treatment of hemolytic streptococcal infections, therapy should continue for at least 10 days to prevent development of rheumatic fever or glomerulonephritis. In the treatment of staphylococcal infections indicated surgical procedures should be carried out in all cases.

Pediatric: A dosage of 3 mg./lb./day in two doses has been found satisfactory in the treatment of most mild to moderately severe infections. For more severe infections, higher dosages may be indicated and should be adjusted accordingly.

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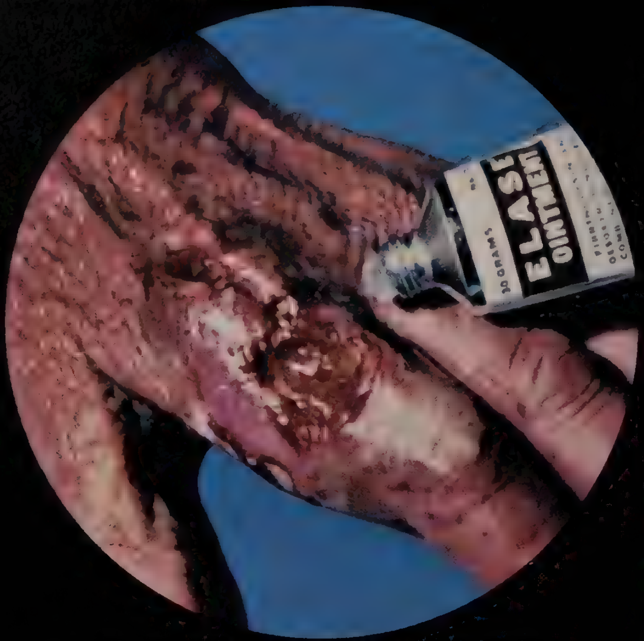
Supply: Terramycin (oxytetracycline) Intramuscular Solution: available in single dose, prescored glass ampules containing 100 or 250 mg. oxytetracycline/2 cc., Isoject® syringes containing 100 or 250 mg. oxytetracycline/2 cc. and 10 cc. multiple dose vials containing 50 mg. oxytetracycline/cc.

More detailed professional information available on request.

this ulcer did not heal...until its surface was cleared of dead tissue and debris



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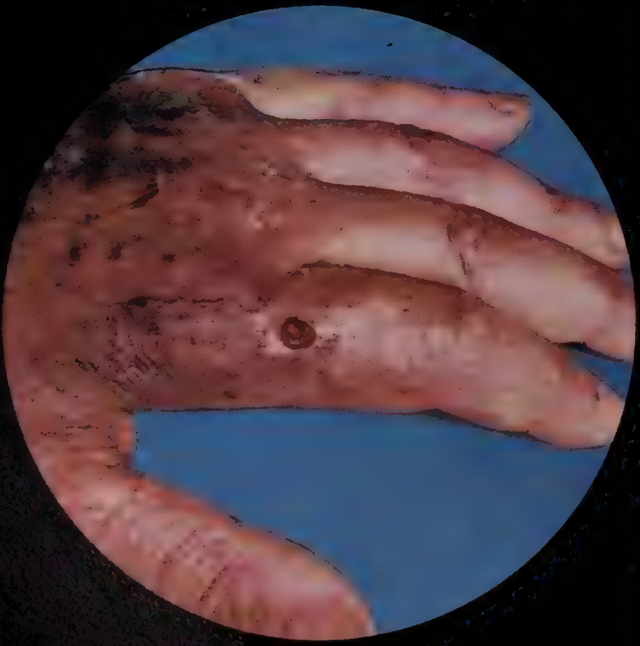
Healing has progressed rapidly without interruption or interference from any accumulated purulence or necrotic tissue. Greatly reduced size of lesion and minimal scar tissue indicate quality and vigor of healing which is almost complete.



to aid in debridement to facilitate healing in chronic cutaneous ulcers...

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(fibrinolysin and desoxyribonuclease, combined, [bovine] ointment)

PARKE-DAVIS

By helping to remove dead tissue and debris from the ulcer's surface, ELASE Ointment creates a better environment for the elimination of infection, for healthy granulation...*for healing.* Its lytic enzymes effectively break down DNA in dead leukocytes and other debris... the fibrin in blood clots, serum, and purulent exudates... and the denatured proteins in necrotic tissue. Protein elements of *living* tissue are relatively unaffected. ELASE Ointment is indicated in stasis ulcers and in other infected or inflamed ulcers caused by circulatory disturbances. In cases requiring skin grafting, it is used preoperatively for debridement. For ambulatory patients debridement with ELASE Ointment is a convenient therapy and a regimen likely to be followed. *Precautions:* Observe usual precautions against allergic reactions, particularly in persons with a history of sensitivity to materials of bovine origin or to mercury compounds. *Adverse Reactions:* Side effects attributable to the enzymes have not been a problem at the dose and for the indications recommended. *Discussion:* Successful use of enzymatic debridement depends on several factors: (1) dense, dry eschar, if present, should be removed surgically before enzymatic debridement is attempted; (2) the enzyme must be in constant contact with the substrate; (3) accumulated necrotic debris must be periodically removed; (4) the enzyme must be replenished at least once daily; and (5) secondary closure or skin grafting must be employed as soon as possible after optimal debridement has been attained. It is further essential that wound-dressing techniques be performed carefully under aseptic conditions and that appropriate systemically acting antibiotics be administered concomitantly if, in the opinion of the physician, they are indicated. *Available:* ELASE Ointment is supplied in 30-Gm. tubes containing 30 units (Loomis) of fibrinolysin and 20,000 units of desoxyribonuclease with 0.12 mg. thimerosal (mercury derivative); and in 10-Gm. tubes containing 10 units of fibrinolysin and 6,666 units of desoxyribonuclease with 0.04 mg. thimerosal. ELASE Ointment has a special base of liquid petrolatum and polyethylene; contains sodium chloride and sucrose used during manufacture; is stable at room temperature through the expiration date stated on the package.

Parke, Davis & Company, Detroit, Michigan 48232

PARKE-DAVIS

48168

Special Article

A New Low-Dose Combination Oral Contraceptive*

EDWARD T. TYLER, M.D.†
Los Angeles, California

SINCE 1956, THE Family Planning Clinics of Greater Los Angeles have been studying a variety of ovarian hormone contraceptive preparations. The first progestogen-estrogen combination that we employed was one containing 10 mg. of norethindrone with .06 mg. mestranol. Shortly after this we initiated investigations of a preparation containing 10 mg. of norethynodrel and .15 mg. of mestranol. Since that time we have used a variety of additional norethindrone-mestranol combinations, as shown in Table 1.

While most of the combinations listed have been clinically very satisfactory, we have been constantly striving to find the optimal ratios of progestogen and estrogen. A major reason for our continued investigations has been the undesired breakthrough bleeding and a few other side-effects common to all contraceptive hormonal agents. While in our experience breakthrough bleeding has been relatively low with norethindrone-mestranol 1/50, it is a little greater than has been our experience with the higher dose preparations. The ratio as well as the amounts of each hormonal ingredient in oral contraceptive tablets may play a significant role in the incidence of subjective side-effects. In an attempt to determine whether an increased amount of estrogen might make a difference, a clinical trial was begun about two years ago with a preparation containing 1 mg. norethindrone with .08 mestranol (1/80).‡

TABLE I
Family Planning Centers, Los Angeles

Sequence of Hormonal Doses			
Late 1940's —	Early 1950's	EE* (alone)	.05 mg.
1956 plus	Norethinedrone	10 mg. + EE3ME†	.06 mg.
	Norethynodrel	10 mg. + EE3ME	.15 mg.
Late 1950's	Norethinedrone	5 mg. + EE3ME	.075 mg.
	Norethynodrel	5 mg. + EE3ME	.075 mg.
Early 1960's	Norethinedrone	2 mg. + EE3ME	0.1 mg.
	Norethynodrel	2.5 mg. + EE3ME	0.1 mg.
Mid 1960's	Norethinedrone	1.0 mg. + EE3ME	.05 mg.
	Ethynodiol Diacetate	1.0 mg. + EE3ME	0.1 mg.
	Chlormadinone *Alone*	.5 mg.	
1966	Norethinedrone	0.5 mg. + EE3ME	0.1 mg.
1966	Ethynodiol Diacetate	0.5 mg. + EE3ME	0.1 mg.
	Norgestrel	0.5 mg. + EE	.05 mg.
1967	Norethinedrone	.35 mg. *Alone*	
	Ethynodiol Diacetate	.25 mg. *Alone*	
	Norgestrel	.075 mg. or .062 mg. *Alone*	

*Ethinyl estradiol
†Ethinyl estradiol, 3-methyl ether

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*Presented at the Annual Meeting of the Canadian Fertility Society, Calgary, Alberta, Canada, July 1968.

†Medical Director, Family Planning Centers of Greater Los Angeles.

‡Ortho-Novum 1/80 supplied for this study by the Ortho Research Foundation.

Nature of the Study

This report relates specifically to the results with this particular low-dose preparation during the first two years of trial. This new low-dose tablet is prescribed one tablet daily for 21 days beginning on the fifth day of the menstrual cycle. After the first cycle, the tablets are taken in the cyclic routine of "three weeks on-one week off."

Physically Normal Applicants

All patients in this study were women who requested oral contraceptives from the Family Planning Centers of Greater Los Angeles, California. Following complete examination of the breasts, abdomen and pelvis and standard routine laboratory studies, those patients found to be in satisfactory physical condition were included in this study. Those who needed specific attention medically were referred for that care and were not started in this program. Return visits were scheduled for every two, four and six months following the initial visit, and computer forms were filled in for subsequent analysis.

Computerized Data

On each return visit the patient's weight, symptoms, menstrual history and side-effects (if any) were noted and recorded. Repeat pelvic examinations were performed in cases of breakthrough bleeding, vaginal discharge or menorrhagia. Prior to initiating medication, Papanicolaou smears were collected from all patients who had not had smears taken elsewhere within a year.

Number of Cycles Studied

All patients admitted to this study were given an initial supply of tablets. A few did not return after the initial visit, and some made only one return visit thereafter; these are excluded from this report. Eight hundred sixty-two patients representing 4,211 cycles of therapy are included in this study. The average number of completed cycles per patient for the entire group was 4.9. The maximum number of cycles for a patient as of October 1968 was 15 (Table 2).

The patients were of an age range of relative maximal fertility, with 565 (71.7%) being between ages 16 and 27 years, while relatively few, 20 (2.8%), were over 40 years. The average age was 24.9 years. The fertile nature of this group is illustrated by the fact that 75.5% of these patients had had at least one full-term delivery prior to entering the study. Several of the remainder had had pregnancies which did not go to term.

Cycle Control

Maintenance of normal cyclic menstrual bleeding on oral contraceptives is important for many women.

TABLE 2
Cycles of Use Among Patients in Low-Dose Study

Last Cycle Completed	No. of Patients	% of Total	Total Cycles Completed	Total Pts. Per Cycle	Per Cent of Total
1	100	11.6%	100	862	20.5%
2	128	14.8%	256	762	18.1%
3	154	17.9%	462	634	15.1%
4	75	8.7%	300	480	11.4%
5	62	7.2%	310	405	9.6%
6	129	15.0%	774	343	8.1%
7	51	5.9%	357	214	5.1%
8	29	3.4%	232	163	3.9%
9	66	7.7%	594	134	3.2%
10	5	.6%	50	68	1.6%
11	5	.6%	55	63	1.5%
12	42	4.9%	504	58	1.4%
13	9	1.0%	117	16	.4%
14	5	.6%	70	7	.2%
15	2	.2%	30	2	%
Total	862	100.0%	4211	4211	100.0%

Average Number of Completed Cycles Per Patient—4.9 Cycles

Shorter Cycle

In this study the average pre-therapy cycle length was 27.9 days, while the average therapy cycle length was 27.1 days, suggesting an apparent tendency to somewhat shorter cycles. But it should be noted that in questioning patients about their reliability in taking tablets 36.5% (31 of 185 patients) of those showing cycle lengths of less than 25 days had in fact taken tablets incorrectly (Table 3).

TABLE 3

Comparison of Pre-Therapy Cycle Length with Therapy Cycle Length

Pre-Therapy Cycle Length	No. of Patient Cycles	Per Cent of Subtotal	Average Therapy Cycle Length
Irregular	68	1.9%	27.4
Less than 21	18	.5%	27.1
21-24	128	3.6%	27.1
25-26	221	6.3%	27.0
27-29	2511	71.2%	27.1
30-35	580	16.4%	27.2
36-42	3	.1%	27.0
Subtotal	3529	100.0%	
Not comparable	682		
Total	4211		

Average Pre-Therapy Cycle Length 27.9 Days

Average Therapy Cycle Length 27.1 Days

Shorter Flow

A comparison of days of flow before and during therapy reveals that prior to therapy 25.9% of the cycles had a duration of four days of flow, 38.1% a duration of five days. During therapy these figures were reversed in trend to 48.8% and 20.4%, suggesting a mild to moderate decrease in duration of flow. Pre-therapy average was 4.6 days and during therapy, 3.9 days (Table 4). Of the total cycles evaluated 233 (5.5%) were not subject to comparison.

TABLE 4

Comparison of Pre-Therapy with Therapy Days of Flow

	Total	Per Cent
Decrease	1909	45.3%
No change	1266	30.1%
Increase	522	12.4%
Not comparable	514	12.2%

Average Days of Flow Pre-Therapy 4.6 Days

Average Days of Flow During Therapy 3.9 Days

Diminution of Bleeding

Categorizing the amount of flow subjectively as "not stated," "none," "light," "moderate" and "heavy" and assigning these values of 0 to 3, our data indicates that average pre-therapy amount of flow was 2.0, while average amount during therapy was 1.9. Thus, the figures for both duration and amount of flow would suggest a slight diminution in bleeding while on this therapy. This would ordinarily be considered a positive side-effect.

Side-Effects

Spotting

Side-effects that occurred were minimal and of little consequence. It was noted that 62 patients (7.2%) reported spotting during therapy, for a total of 81 cycles (1.9% of cycles). Eleven of these 62 patients reported incorrect tablet-taking during cycles of spotting. Spotting gradually decreased with each cycle. Regarding breakthrough bleeding, this similarly occurred more in the earlier cycles, with an incidence of 1.9% of the total 4,211 cycles, and with 67 patients of the 862 (7.8%) experiencing this during a total of 44 cycles. In 10 cycles this was associated with incorrect taking of the tablets.

Lessening of Dysmenorrhea

Dysmenorrhea, which was a complaint in almost half of the women prior to therapy, was improved in 38.2% of the cycles of therapy, unchanged in 45.7%, increased in only 1.5%; and findings were not comparable in 8.3%. Thus it may be stated in general that the therapy apparently was associated with improvement in dysmenorrhea in a substantial number of cycles.

Decreased Tension

Pre-menstrual tension occurred in about one third of pre-therapy cycles, and during therapy there was a decreased incidence of it in approximately 85.4% of those previously complaining of it.

Gastrointestinal Disturbances

The incidence of gastrointestinal disturbances was very low in this study. Nausea was reported in practically only the first three cycles, 12 patients experiencing it in the first cycle, six in the second, and three in the third. The total number of cycles associated with gastrointestinal disturbances was 29 of 4,211 (incidence of 0.7%). The patient incidence in the total 862 evaluated was 20 or 2.3%.

Weight Change

In weight changes the percentage of patients showing gain (45.9%) and loss (38.6%) was very similar. No weight change was reported in 15.5%; on 256 patients in the group no comparable data were available (Table 5).

A representative sample of patients was used to measure pituitary-ovarian function, liver function, adrenal function, and effects of this combination estrogen-progestogen on cervical mucus.

TABLE 5
Comparison of Pre-Therapy Weight with Last Reported Therapy Weight

	Weight Gain	Weight Loss	Total	% of Subtotal
No change in weight			94	15.5%
1-5 pound change	195	160	355	58.6%
6-10 pound change	55	56	111	18.3%
11-15 pound change	17	11	28	4.6%
16 & over pound change	11	7	18	3.0%
Subtotal	278	234	606	100.0%
Per cent of comparable patients	45.9%	38.6%		
Patients not comparable			256	
Total in study			862	

Urinary gonadotrophin determinations were done on 10 patients. All determinations were within normal limits. Twenty-four hour urine collection was made for four consecutive days on each of 12 patients, who on the third day were given 750 mg. metapirone every four hours. The responses to metapirone were normal in every case tested.

The finding of luteal-type cervical mucus on 22 patients suggests an additional contraceptive effect. This type of mucus tends to inhibit spermigration.

Effectiveness

One pregnancy, which was unplanned, occurred during this study in 4,211 cycles, or 351 women-years. This suggests a pregnancy rate of 0.28, which is one of the lowest reported for any of the oral contraceptives.

Summary

It appears that on the basis of the number of women studied, the degree of effectiveness, and the relatively low incidence of side-effects that a preparation containing a low-dose of norethinedrone 1 mg. with mestranol 0.08 mg. is a very good oral contraceptive.

Vision

A man once found a shiny new dime in the road. From then on his mind was focused on small things and he never lifted his eyes from the ground while walking. At the end of forty years, he accumulated 34,947 buttons, 54,712 pins, 11 pennies, a bent back and a bad disposition. He lost the glories of the light, the smiles of friends, the beauties of nature, and the opportunity to serve his fellowmen and spread happiness.*

---

*Alexander Co-operator.

Values

The Arab was telling of the time he had lost his way in the desert. Just as he was about to abandon hope and let his hunger overcome him, he found a bag of pearls. "I shall never forget," he said, "the relish and delight I felt supposing the contents of the bag to be dried wheat, or the bitterness and despair I suffered in discovering that the bag contained nothing but pearls."*

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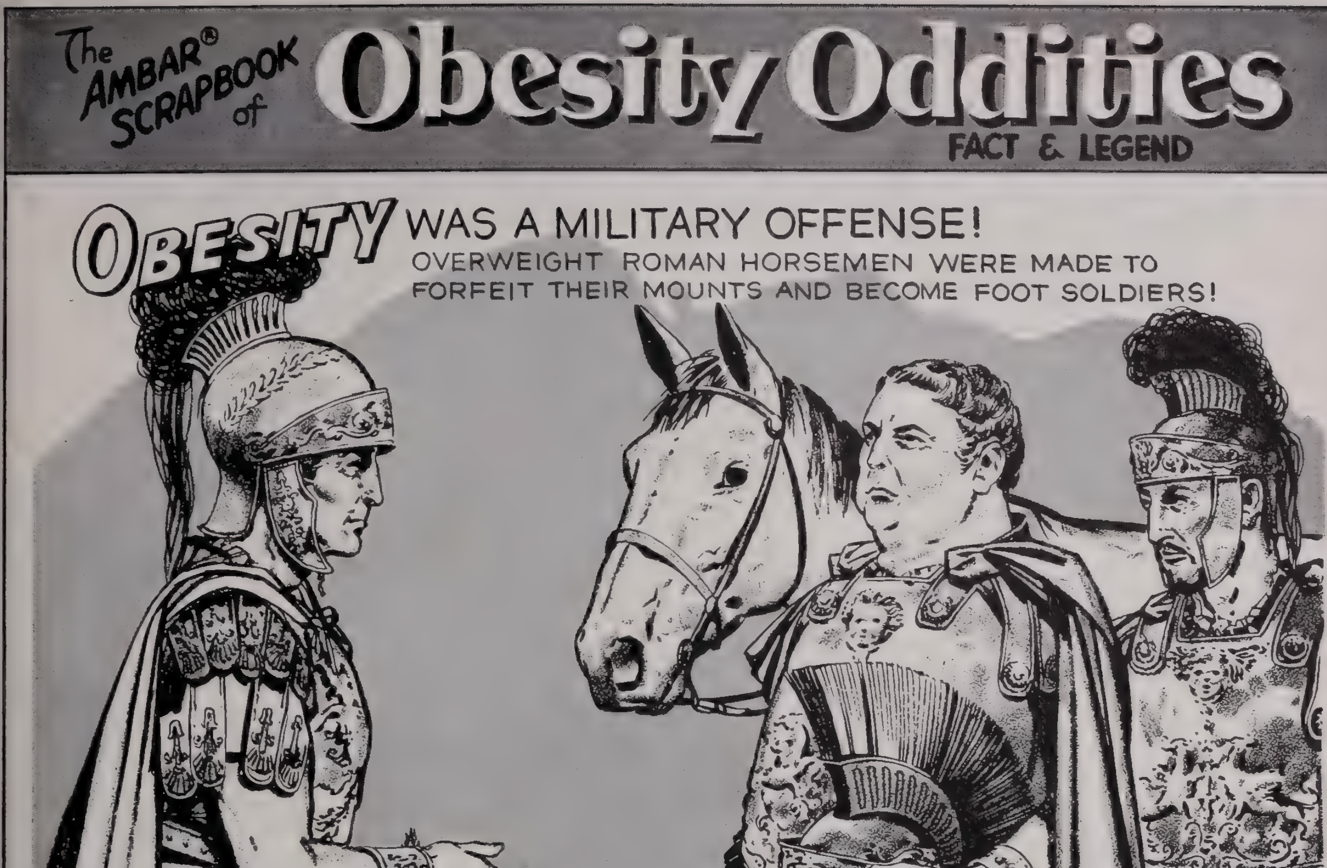
*Red Barrel.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OBESITY WAS A MILITARY OFFENSE!
OVERWEIGHT ROMAN HORSEMEN WERE MADE TO FORFEIT THEIR MOUNTS AND BECOME FOOT SOLDIERS!
RECORDED ON AN ENGLISHMAN'S TOMBSTONE
JAMES PARSON
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HE HAD OFTEN EATEN A WHOLE SHOULDER OF MUTTON AND A PECK OF HASTY PUDDING
SHAKESPEARE WAS AWARE OF THE DANGERS OF OBESITY HE WROTE...
Make less thy body hence
and more thy grace,
leave gormandizing;
Know thy grave doth
gape for thee wider
than for other men.
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THE COST OF AMBAR EXTENTABS IS APPROXIMATELY ONE HALF THAT OF OTHER LEADING APPETITE SUPPRESSANTS
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methamphetamine HCl 15 mg.,
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One Ambar Extentab before breakfast can help control most patients' appetite for up to 12 hours. Methamphetamine, the appetite suppressant, gently elevates mood and helps overcome dieting frustrations. Phenobarbital, the sedative in Ambar, controls irritability and anxiety...helps maintain a state of mental calm and equanimity. Both work together to ease the tensions that erode the willpower during periods of dieting.

Also available: Ambar #1 Extentabs®—methamphetamine hydrochloride 10 mg., phenobarbital 64.8 mg. (1 gr.) (Warning: may be habit forming).

BRIEF SUMMARY/**Indications:** Ambar suppresses appetite and helps offset emotional reactions to dieting. **Contraindications:** Hypersensitivity to barbiturates or sympathomimetics; patients with advanced renal or hepatic disease. **Precautions:** Administer with caution in the presence of cardiovascular disease or hypertension. **Side Effects:** Nervousness or excitement occasionally noted, but usually infrequent at recommended dosages. Slight drowsiness has been reported rarely. See package insert for further details.

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heavenly relief
for unearthly cough

Benylin®
EXPECTORANT

Each fluidounce contains: 80 mg. Benadryl® (diphenhydramine hydrochloride, Parke-Davis); 12 grains ammonium chloride; 5 grains sodium citrate; 2 grains chloroform; 1/10 grain menthol; and 5% alcohol. An antitussive and expectorant for control of coughs due to colds or of allergic origin, BENYLIN EXPECTORANT is the leading cough preparation of its kind. BENYLIN EXPECTORANT tends to inhibit cough reflex... soothes irritated throat membranes. And its not-too-sweet, pleasant raspberry flavor makes BENYLIN EXPECTORANT easy to take. PRECAUTIONS: Persons who have become drowsy on this or other antihistamine-containing drugs, or whose tolerance is not known, should not drive vehicles or engage in other activities requiring keen response while using this preparation. Hypnotics, sedatives, or tranquilizers if used with BENYLIN EXPECTORANT should be prescribed with caution because of possible additive effect. Diphenhydramine has an atropine-like action which should be considered when prescribing BENYLIN EXPECTORANT. ADVERSE REACTIONS: Side reactions may affect the nervous, gastrointestinal, and cardiovascular systems. Drowsiness, dizziness, dryness of the mouth, nausea, nervousness, palpitation, and blurring of vision have been reported. Allergic reactions may occur. PACKAGING: Bottles of 4 oz., 16 oz., and 1 gal.

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Detroit, Michigan 48232

PARKE-DAVIS

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Book Reviews

That is a good book which is opened with expectation and closed with profit.
—Alcott

PRACTICAL PSYCHIATRY FOR INTERNISTS —Douglas Goldman, George A. Ulett; C. V. Mosby, 1968; 168 pp. $9.85.

Internists are aware of the heavy percentage of neurotic and psychiatric problems among their patients. In my practice about 75% of the patients are seen for such difficulties. If one adds those with "organic" complaints, but who also have important psychological aspects, the figure approaches 100%. This book is a primer written by psychiatrists for internists and general practitioners. Its brevity, 168 pages, commends itself to busy physicians. Occasionally it is too brief. In their attempt to put across the idea that emotional influence induce the formation of gallstones, the case histories the authors adduce are confined to the statement that three female employees (of the offending cholelithogenic physician) and his maid *required* cholecystectomies. It is unfortunate that this book, which contains so many concepts so important to internists, should also contain such untenable ideas as this gallstone theory. Collaboration with a physician would have at least required that their thesis be defended with enough data to establish the pathological facts. Did the girls have gallstones?

The chapter on frank psychiatric disorders with numbers keying the diagnoses to the International Classification of diseases will interest chiefly those preparing for examination in the field.

Hypnosis in medicine is briefly discussed. The book can serve a useful purpose to internists and others who must learn to appreciate the major aspects of psychiatry in medicine.

Reuben Berman, M.D.
Minneapolis, Minnesota

WHAT YOU CAN DO ABOUT CANCER. Joseph C. Maroon, M.D., Doubleday & Co., Inc., 1969. Price: $5.95.

This is a well-written book by a physician giving some interesting facts about some of the most commonly encountered types of cancer. At the end of each chapter he provides answers to some of the most commonly encountered questions. This book should provide its greatest value to the lay reader of medical topics.

Carl O. Rice, M.D.
Minneapolis, Minnesota

MASTERS OF MEDICINE, AN HISTORICAL SKETCH OF THE COLLEGE OF MEDICAL SCIENCES, UNIVERSITY OF MINNESOTA, 1888-1966.

A 940-page history of the University of Minnesota's College of Medical Sciences has been published—the culmination of six years' research and writing by its author, Dr. Jay Arthur Myers, professor emeritus of internal medicine and public health.

The work, which includes some 245 pictures—was made possible by a $20,000 gift from Dr. Frank McKinney to the Minnesota Medical Foundation. Dr. McKinney, a Minneapolis surgeon, practiced with Dr. Myers, a 1920 graduate of the University's Medical School.

DYSLEXIA: DIAGNOSIS AND TREATMENT OF READING DISORDERS. Edited by Arthur H. Keeney, M.D., and Virginia T. Keeney, M.D. C. V. Mosby Company, St. Louis. 1968. Price: $12.00.

During the last two years remarkable advances have been made in the knowledge of diagnosis and treatment of reading disorders. The physician, educator, or therapist seeking new knowledge in the field of dyslexia had previously been required to search the literature in a wide range of fields to come across the published papers. "Dyslexia," which is a summation of a National Conference on dyslexia held at Philadelphia, Pennsylvania, fills a great need for such individuals who require current up-to-date knowledge on this subject. The fourteen authors who contributed to this volume write with a uniformity and clarity which indicates careful editing. General areas include definition, etiology, pathophysiology, clinical detection, treatment, and psychological problems, and finally a discussion of topics worthy of research.

The summary of discussions, "Questions and Answers," points out problems not fully appreciated by the authors and the need for new areas of research and endeavor. By large, this is an excellent book and worthy of study by all physicians and paramedical workers who deal with children with a reading disability.

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Dosage: One 350 mg. capsule, 3 times daily and two at bedtime is suggested as the adult starting dose. Adjust to suit individual requirements. Daily doses above 3000 mg. are not recommended.

Contraindications: Known hypersensitivity to tybamate. Since no studies have been done with this drug in human pregnancy, it should not be used in pregnancy unless the potential benefit outweighs the risk.

Warnings: Administer cautiously to patients receiving phenothiazines or other CNS depressants or having history of convulsive seizures (See Adverse Reactions). Consider possibility of additive actions with alcohol or other psychotropic agents, particularly phenothiazines or MAO inhibitors.

Precautions: Avoid abrupt withdrawal after prolonged use, although withdrawal symptoms have not been reported to date. Exercise caution in addiction-prone individuals. If symptoms of hypersensitivity occur, discontinue at once and initiate appropriate symptomatic treatment. Avoid activities requiring optimal mental alertness if drowsiness or vertigo are present. As with any new drug, use cautiously in patients with history of drug allergies, blood dyscrasias, and hepatic or renal disease; periodic measurements of hepatic, hematopoietic and renal function should accompany prolonged and/or high doses.

Adverse Reactions: Most frequent reactions, rarely requiring discontinuation of tybamate, include drowsiness, dizziness, nausea, insomnia, and euphoria. There have been a few reports of skin rash, urticaria, and pruritus. Rare side effects include hyperactivity, fidgetiness, flushing, and tachycardia, suggesting excessive stimulation; also ataxia, unsteadiness, confusion, feeling of unreality, "panic reaction," fatigue, headache, paresthesias, vertigo, gastrointestinal disturbances, glossitis, and dry mouth. Grand mal or petit mal seizures have been reported in a few hospitalized psychotic patients receiving tybamate (up to 6000 mg. daily) together with phenothiazines and other psychotropic agents, but not with tybamate alone. Consider the possibility of rare, serious adverse reactions such as may occur with the related drug, meprobamate. If excessive amounts are ingested, gastric lavage and symptomatic therapy, including central stimulants as necessary, are recommended. Before prescribing, consult package circular.

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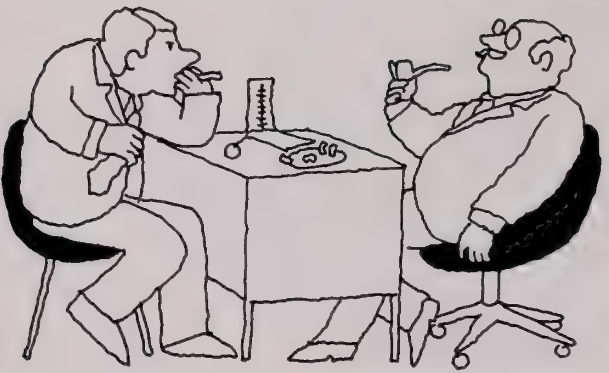
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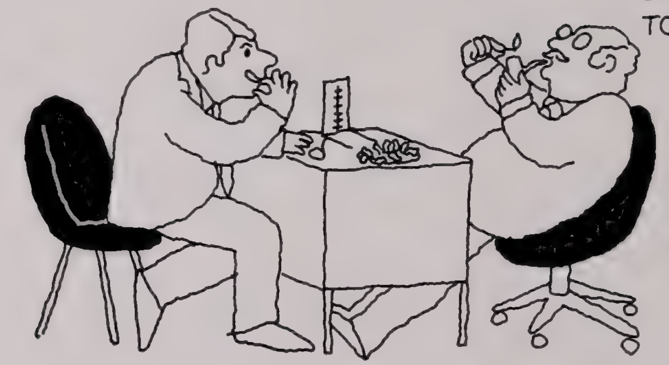
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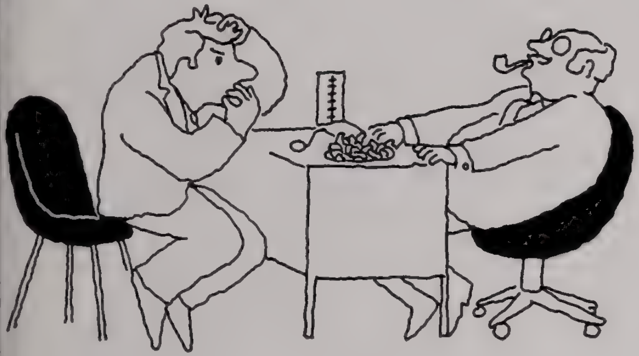

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corticosteroids, ACTH, or digitalis. Severe salt restriction is not recommended. Use cautiously in patients with ulcerative colitis or gallstones (biliary colic may be precipitated). Bronchial asthma may occur in susceptible patients. *Adverse Reactions:* The drug is generally well tolerated. The most frequent side effects are nausea, gastric irritation, vomiting, diarrhea, constipation, muscle cramps, headache, dizziness and acute gout. Other potential side effects include angina pectoris, anxiety, depression, bradycardia and ectopic cardiac rhythms (especially when used with digitalis), drowsiness, dull sensorium, hyperglycemia and glycosuria, hyperuricemia, lassitude, restlessness, transient myopia, impotence or dysuria, orthostatic hypotension which may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics, leukopenia, aplastic anemia, skin rashes, thrombocytopenia, agranulocytosis, nasal stuffiness, increased gastric secretions, nightmare, purpura, urticaria, ecchymosis, weakness, uveitis, optic atrophy and glaucoma, and pruritus. Eruptions and/or flushing of the skin, a reversible paralysis agitans-like syndrome, blurred vision, conjunctival injection, increased susceptibility to colds, dyspnea, weight gain, decreased libido, dryness of the mouth, deafness, anorexia, and pancreatitis when epigastric pain or unexplained G.I. symptoms develop after prolonged administration. Jaundice, xanthopsia, paresthesia, photosensitization and necrotizing angiitis are possible. *Average Dosage:* One tablet daily with breakfast. *Availability:* Pink, single-scored tablets in bottles of 100 and 1000. (B)46-600-C

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Minnesota Medicine at a Glance

Anesthesia after Myocardial Infarction—*Tarhan and Moffitt* Page 1733.

The steps to avoid operational and postoperative cardiac complications are discussed in this concise article concerning the high-risk patient with a recent myocardial infarction.

Hepatic Coma—*Lindall et al.* Page 1737.

The authors report the case of a pregnant patient successfully treated by multiple exchange transfusions for a fulminant hepatic coma secondary to infectious hepatitis. Although 82 cases of hepatic coma have been treated by exchange transfusion, this is only the second case reported in pregnancy. In addition to the exchange transfusions, conventional measures were also employed.

Coronary Care in a Small Hospital—*Anderson* Page 1741.

An intensive coronary care unit (ICCU) was established in a very small community hospital whose staff was made up of eight private practitioners, all generalists. A mortality of 18% was observed in 33 cases of acute myocardial infarction as compared to a mortality of 46% in 24 cases during one year prior to the establishment of the ICCU. The unit was used for 52 other patients during the year who likewise benefited from the intensive care. The very small community hospital can develop and effectively operate a coronary unit with gratifying results.

Prolonged Oxygen Therapy—*MacDonald et al.* Page 1745.

Distinctive morphologic pulmonary lesions associated with prolonged oxygen therapy at high concentrations were observed in 20 patients who came to autopsy in 1966, nineteen of whom had had assisted ventilation for three to 120 days. The 20th patient had breathed for four days from a mask which delivered 100% O_2. All had an inappropriately low partial pressure of oxygen in their arterial blood.

Histologically, the distinctive pattern in the lung included intra-alveolar deposits of fibrin, hyaline membranes, thickened intra-alveolar septa, prominent alveolar lining cells, and chronic inflammatory cellular infiltrate of variable degree. This morphologic pattern was not associated with pulmonary edema, organizing pneumonia, and bronchopneumonia of various etiologies.

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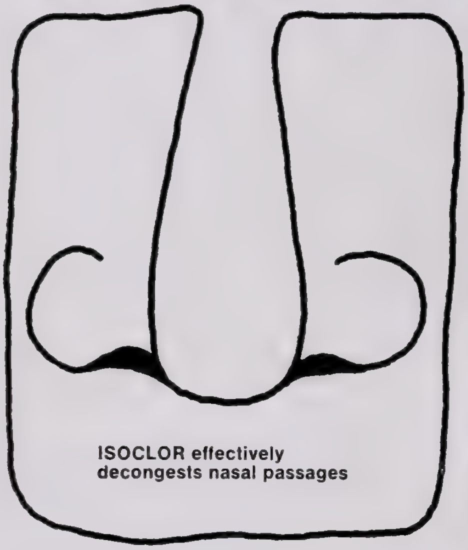
tr Morning" *Robert C. Knutson, M.D.*

DECEMBER, 1969

Special Issue
Minnesota Radiologic Society

HERE ARE THE COLD FACTS: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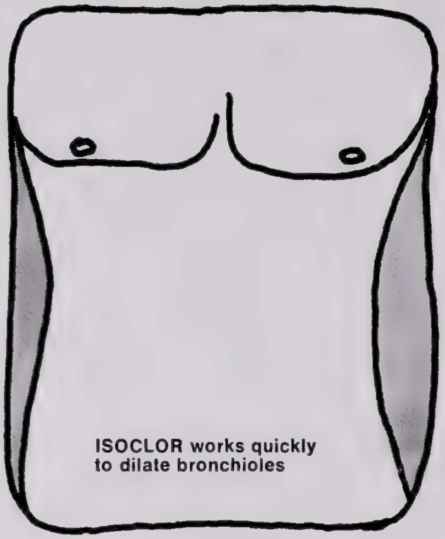
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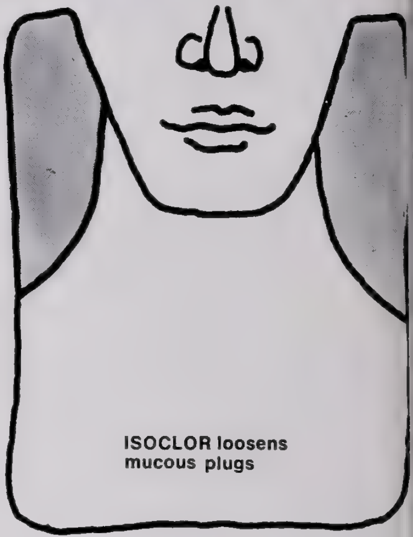
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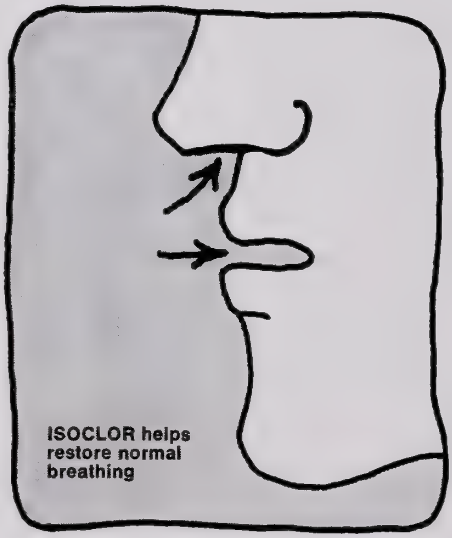
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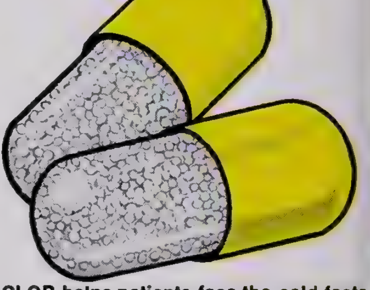
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In a special pellet form providing both prompt and sustained effect.

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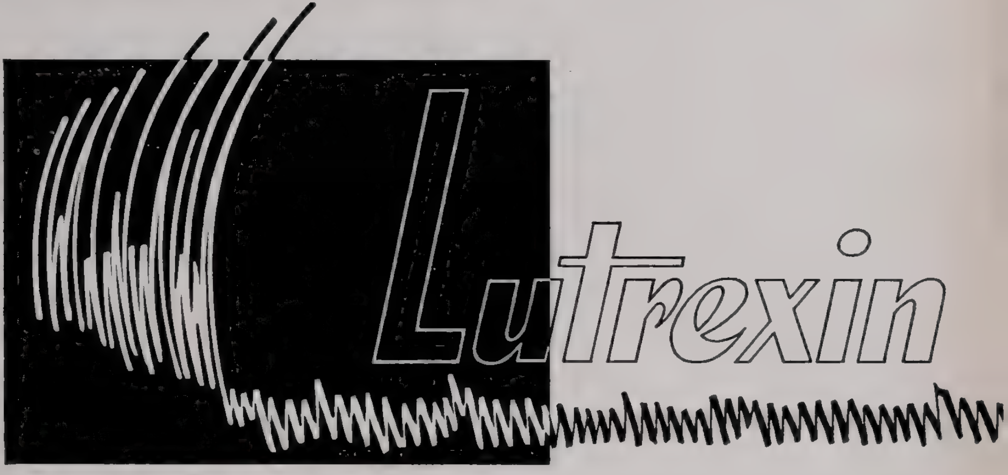

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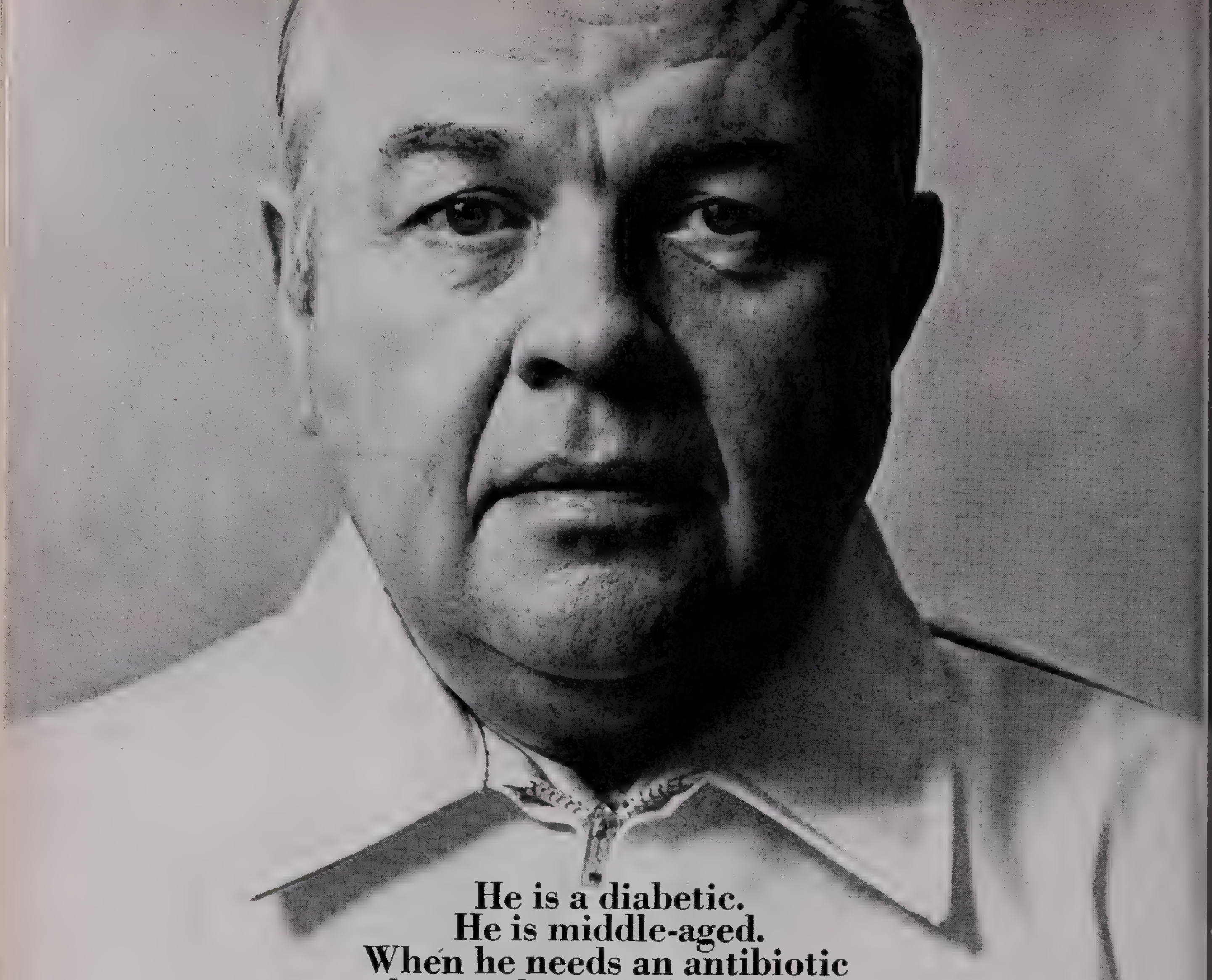

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Precautions: Overgrowth of nonsusceptible organisms may occur. Constant observation is essential. If new infections appear, appropriate measures should be taken. In infants, increased intracranial pressure with bulging fontanels has been observed. All signs and symptoms have disappeared rapidly upon cessation of treatment.

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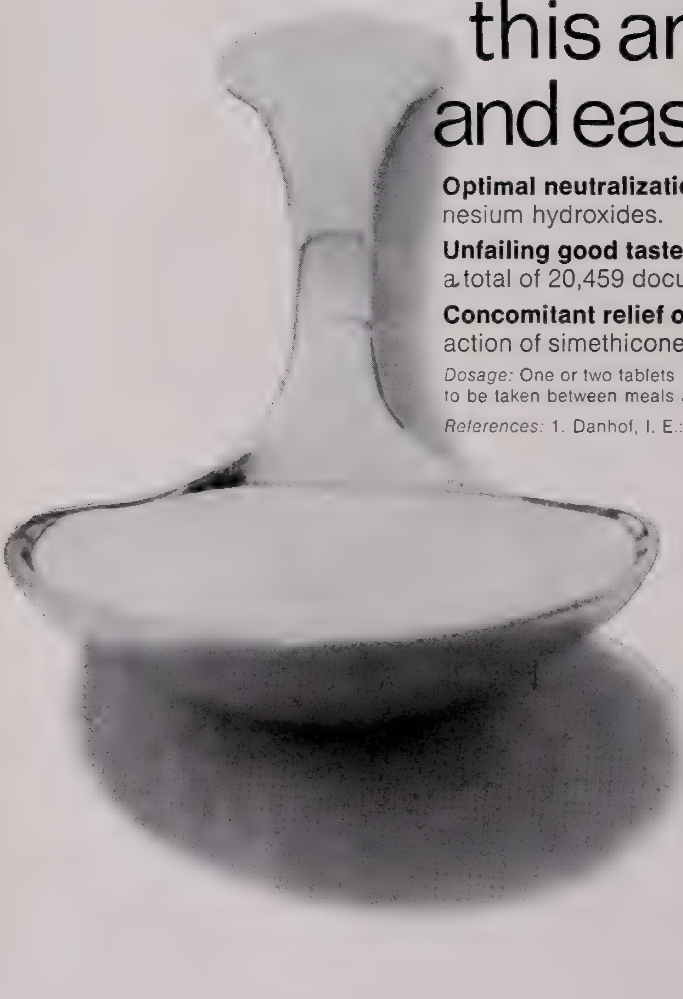

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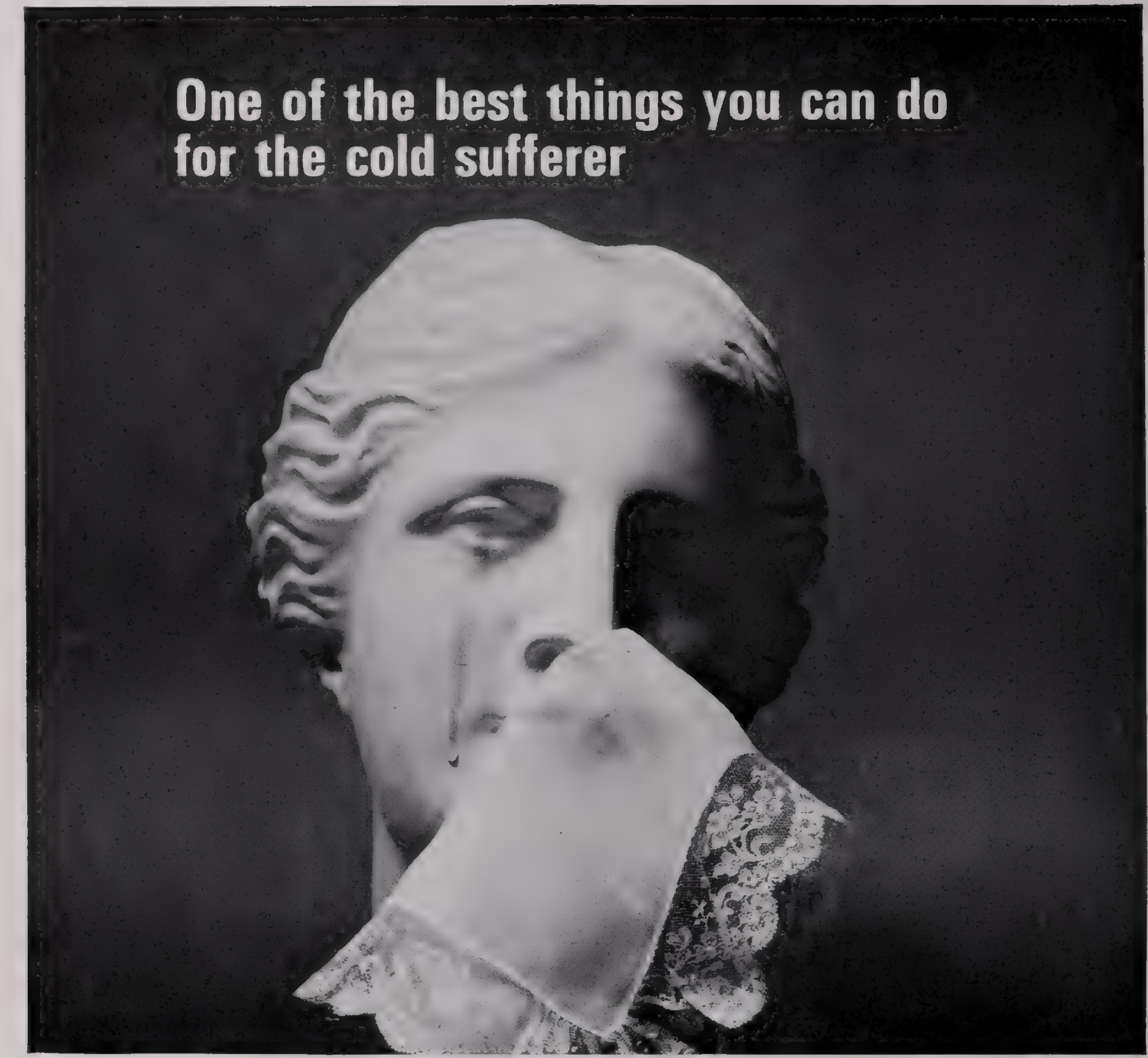
See the President's Letter, Page 1855.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President's Letter

Identity

Preoccupation with identity has pervaded religious and philosophical thought throughout recorded history.

The radiologist is now engaged in a struggle for professional identity—to be associated with the family doctor, surgeon, and other specialists in the eye of the general public.

Recognition of the radiologist's worth and place in medical practice has been well established within the profession.

Outside the profession few are informed as to his area of knowledge, skill, and discipline, and how it applies to them as patients. This has been the fault of the radiologist himself for following the path of least resistance and allowing the hospital to front for his activities and to collect for his services under the broad heading of "X-rays" or "X-ray Department."

A national movement by radiologists, given urgency by the Medicare legislation, got under way in July, 1966, whereby the radiologist has emerged from anonymity by billing directly for his services. This has by no means been embraced by all the specialty; but the way has been shown, and the results are heartening and satisfying.

It is only right that the radiologist should bear the responsibility for his fees, his diagnoses, and his decisions. It is only right that the affected person know where the responsibility rests. It is only just that none hide behind the hospital facade and let the public get the mistaken idea that the hospital can practice medicine. This is truth in packaging.

"The hospital is primarily a building in which patients are housed, fed and rendered medical care by physicians and their technical assistants."* When the public knows who the radiologists and other hospital-based specialists are and that their technical assistants are of necessity trained by the medical profession, there will be no confusion as to who administers health care: the hospitals or the doctors.

It is up to us to do our best to set the record straight through the most direct and professional relationship possible, established by direct billing. This in turn means public education: billing, collecting, and explaining. We are remiss if we do not have a printed explanation and a place where our representatives can explain to the public and establish rapport, understanding, and good will.

I have been rarely thanked by the patient for finding pathology, but I now have the satisfaction of being known in my community. Our egos need feeding, too, and we must be prepared to accept blame as well as credit. "Triumph and Disaster", the two imposters of Kipling's poem, are none the less life ingredients.

Now the final step has been taken in the search for identity, and the patient has been billed for services rendered by the doctor rendering the service. This, more than any other factor, has established the relationship of the practice of radiology to the practice of medicine and identified the radiologist with the physician.

Out of this is emerging a newly earned sense of self-respect with a growing public awareness of the radiologist and the part he contributes to the practice of medicine.

R. L. Pedersen, M.D.
President
Minnesota Radiological Society

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*A Guide For Radiologists, Page 4, 1969.

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Volume 52

Number 12

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R. L. Pedersen, M.D. 1855

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The Appearance of Iliac Crest Epiphysis

An Indicator of Gonadal Dysfunction

DONALD E. DIETRICH, M.D.[*]
St. Paul, Minnesota

OSSIFICATION AND closure of the iliac crest epiphysis has often been reported to be an indicator of gonadal function. Other epiphyses which appear in adolescent years, but which have not received the attention of the iliac crest, include the ischial tuberosity, the os acetabulum of the hip, the acromion of the clavicle and accessory epiphyses, the coracoid process of the scapula and the epiphyses of the fingers.[7,13] The purpose of this paper is to emphasize the relationship of the iliac crest epiphysis to gonadal dysfunction.

Numerous authors have concluded that ossification of the iliac crest epiphysis is related to puberty. In 1942 Buhl and Pyle[7] suggested that onset of ossification of the crest of the ilium might be used as a maturity determinator in adolescence, inasmuch as it occurred within six months of menarche[†] in two thirds of girls. They also determined that boys follow girls in this sequence of ossification by an average of 1.6 years. In 1961 Hewitt and Acheson[17] concluded that maturation of the pelvis is more responsive to the hormonal changes of puberty than that of the femur. Palma et al. in 1967[25] established that ossification of the iliac epiphysis occurs at puberty, during the year of maximum growth, plus or minus a year. They found that this epiphysis was present in the majority of girls having spontaneous or therapeutically induced menstrual periods. "This indicates that its appearance is an index of hormonal modification peculiar to puberty." Garn, Rohmann and Silverman[13] stated that in puberty more attention must be given to the hip and the sesamoids of the thumb and other fingers, and Silverman[31] concluded that iliac crest ossification occurs in a significant population within six months of the onset of puberty, and that fusion with the primary centers occurs within a few years following ossification development.

Numerous authors have offered standards of postnatal ossification and closure[1,7,8,10,11,13,14,18,23,26] and many tables are extended to include adolescent years. Statistically, Garn, Rohmann and Silverman[13] have determined the median and significant deviation of most ossification centers. The chronological age of appearance of the iliac crest epiphysis is given in Table 1.

[†] See Test Your Word Score, Page 1921.

[*] Presently located at the Maui Memorial Hospital, Wailuku, Maui, Hawaii.

The Functional Prepuberal Castrate Syndrome (Testicular Agenesis)

This syndrome is unique as it affords an opportunity to visualize by x-ray the effect of testosterone on epiphyseal centers. Patients are male phenotypes* who have not developed normal testes. Biopsy may reveal remnants of wolffian duct derivatives or hyalinized prepuberal testes.[35] There is a secondary delay in skeletal maturation, and these patients exhibit greater growth in the lower half of the body. They show failure of development of the external genitalia as well. Since gonadal tissue is not present there is no response to endogenous or exogenous gonadal stimulation.[15]

Case Report

A 28-year-old man presented himself for a premarital physical examination, stating that libido was satisfactory. An excretory urogram was requested as part of the medical workup and, because of radiographic findings, further studies were undertaken (Figures 1, 2, 3).

Past history was that at age seven he was suspected of having bilateral undescended testes but at surgery was found to have congenital nondevelopment of both testicles. During his early years he was of small stature but, at about age 13, a growth spurt was noted; at age 18 he was six feet tall and at 21, six feet, three inches, weighing 220 pounds. He denied weakness or color blindness and stated that he shaved two or three times a week.

Family history was unremarkable. His mother was twenty years of age at the time of the patient's birth.

Physical examination revealed a moderately obese Caucasian male with a boyish face and a high-pitched voice; height 76 inches, total breadth of arm span 79 inches.

There was no chest hair, sparse axillary hair and a female escutcheon.

The penis was atrophic; no palpable testes or herniations were detected. Roentgenograms (Figure 1) reveal moderate ossification of the iliac crest epiphysis but no fusion. There is a borderline metacarpal sign (Figure 2) but no evidence of genu valgum. Laboratory findings are listed in Table 2 and Figure 3.

After eight months of oral testosterone medication, his shaving habits have increased from two or three times a week to daily. Follow-up x-rays revealed only slight improvement in right iliac crest epiphysis.

Hypogonadism

No available classification of hypogonadism is entirely satisfactory or complete, but gonadal dysfunction is usually classified into two main groups: 1, Primary gonadal deficiency with elevated gonadotropin, and 2, hypothalamic or pituitary insufficiency.

Eunuchoidism is seen in both sexes, though decreased function is more often found in the female.[5] Most frequently eunuchoidism results from surgical removal of gonads in childhood or from a disorder which causes the gonads to atrophy or be destroyed before puberty.[9] It has

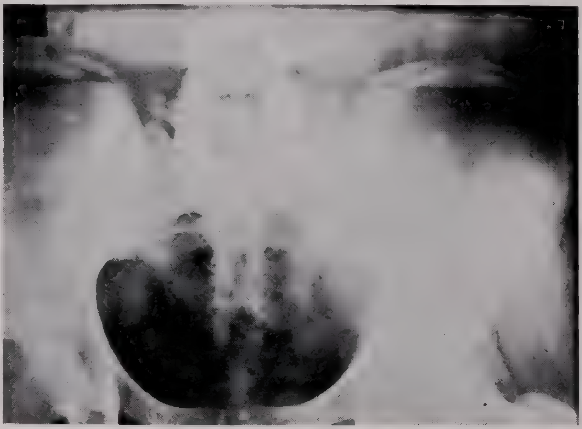

Fig. 1—Epiphysis of iliac crest at age 28—an indication of gonadal dysfunction, A-P, pelvis.

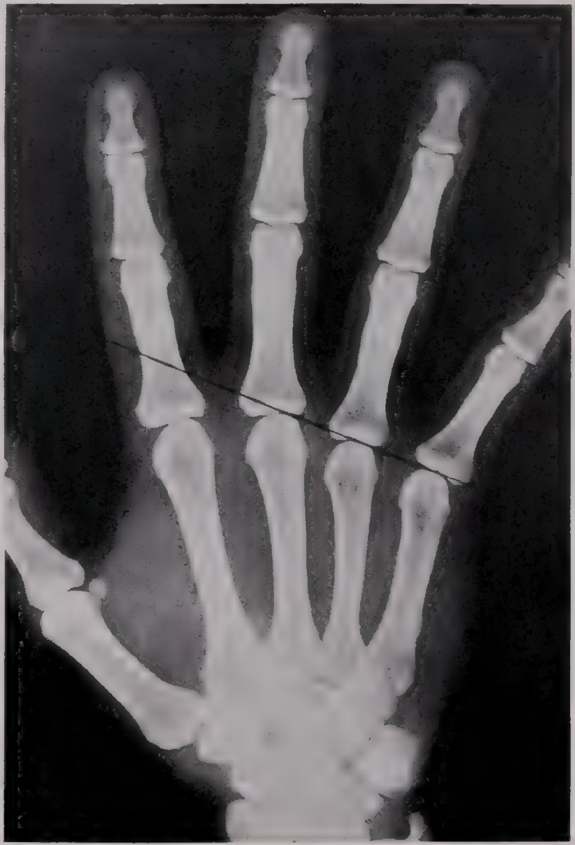

Fig. 2—Metacarpal sign—borderline. A-P, right hand.

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*See Test Your Word Score Page 1921.

been established that as a result of gonadal androgen deficiency in childhood, there is delay in epiphyseal closure, resulting in retarded maturation.[15] The effects of maturation are greater than on linear growth.[34]

Castration

The experimental effects of castration on the mammal depend upon the age when the operation is performed. Thus, if gonads are removed before puberty, accessory sex organs and secondary sex characteristics fail to develop and there is a greater deposition of fat. It has been recognized that castration of boys prior to puberty retards ossification of the epiphysis of the long bones; the persistence of epiphyseal synarthrosis* creates a disproportionment characterized by lengthening of the lower limbs[5,30]

Associated Disorders

Hypogonadism may be accompanied by varying degrees of gynecomastia, cryptorchidism and menstrual abnormalities as well as delayed puberty. It is often part of such disorders as the Laurence Moon Biedl syndrome, mental defectiveness, Friedreich's ataxia, myotonia dystrophica, progressive muscular dystrophy, amyotonia, Werner's syndrome, dyskeratosis congenita (Zentrical-Cole-Engman's syndrome), ichthyosis, etc.[15]

Endocrine Dysfunctions

The determination of urinary gonadotropins will differentiate pituitary from primary testicular or ovarian dysfunction. The determination of 17-ketosteroids is popular but has little value inasmuch as 70% originates from precursor secreted by the adrenal cortex; hence, this is not a true test of testosterone or estrogen production.

TABLE 1
Epiphysis of the Iliac Crest
Age of Appearance in Years
(Percentile)

	5th	50th	95th
Boys	12.03	14.03	15.91
Girls	10.81	12.97	15.31

*Garn Rohmann and Silverman. Med Rad and Photo 43:2, 1967.

TABLE 2
Laboratory Work November 30, 1967

CHROMATIN SEX
Buccal smears—500 cells examined, no barr cells
Blood smears —400 cells counted, no drumsticks
Therefore male pattern

CHROMOSOME ANALYSIS—46 with X and Y chromosomes
Therefore normal male karyotype

PBI: 5.0 mcg%	(Normal 4-8 mcg%)
17 K.S.: 11.1 mg/24 hrs.	(Normal 3-14 mg)
FSH: 48-96	(Normal 6-48)

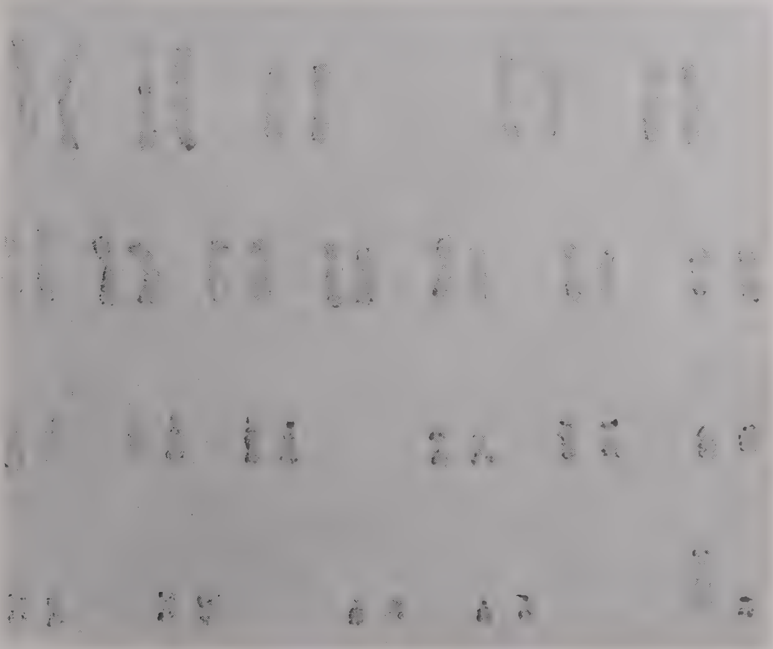

Fig. 3—Chromosome typing—normal male.

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*See Test Your Word Score Page 1921.

Plasma and Urine

Plasma and urinary testosterone levels permit a specific assessment of Leydig cell function. These values have increased our understanding of hypogonadism and secondary effects[24,29,35]; when Leydig cell function is deficient, androgen replacement therapy is indicated.

Numerous studies have shown that estrogens in large amounts will artificially decelerate growth in rodents and humans.[2,30,35] In gonadal dysgenesis, because of lack of estrogen, growth continues through puberty for a longer period than in a girl who feminizes. When estrogen is lacking, the extremities tend to be excessively long and the patients may be tall, implying delayed epiphyseal closure in the female. When estrogen substitution therapy is used, as in the artificial deceleration of growth, the effect is not immediate but growth tends to be decelerated. If such a patient is dwarfed, however, it is advisable[35] to defer substitution therapy for as long as possible in order to achieve maximum stature.

Urinary estrogen excretion products and the plasma levels of estrogen determined by chromotography are valuable research techniques; however, the expense of these studies renders them impractical.[35]

Hypergonadism

Accelerated Maturation

With increased gonadal function, there is accelerated maturation, and dwarfism can result from early closure of the epiphyseal centers.[3] Although the direct mechanism is not known, androgens are known to support osteoblastic elaboration of octeoid, thus stimulating endochondral as well as intramembranous bone growth.

Precocious Puberty

Often the true cause of precocious puberty is unknown. Accelerated maturation is present in the adrenogenital syndrome.[5] A condition which causes sexual precocity in females and deserves special consideration is the granulosa cell tumor of the ovary. Five percent of patients with this condition are under fifteen years of age and experience accelerated maturation with advanced bone age.[9] Precocious puberty may also be seen with rare adrenal cortical tumors, ovarian tumors and hypothalmic lesions.[19,35] Patients whose ovaries are stimulated by gonadotropin have advanced bone age and excessive growth. However, the advancement of bone age is usually not as great as it is in children who have large amounts of estrogen produced by tumors.[35] Albright's syndrome may be associated with precocious puberty in the female. In these cases also, there may be early appearance of ossification centers and closure so that growth stops—often resulting in dwarfing of stature.[9]

Gonadal Dyscrasias

Recent rapid expansion of knowledge in genetics has brought to the radiologist's attention a number of disorders associated with aberrations of chromosomal constitution. Radiographic findings have been summarized by numerous authors[12,16,21,22,24] There are differences of opinion in the literature as to whether or not there is delayed osseous maturation accompanying gonadal dysgenesis.[23]

Seminiferous Tubular Dysgenesis

Klinefelter's syndrome (seminiferous tubular dysgenesis) (XXY) is possibly the commonest cause of infertility in man, and the eunuchoidal features are often first found in puberty.[15] Tanner feels that the skeletal proportions cannot be attributed to delayed epiphyseal fusion since skeletal maturation follows a normal male pattern.[34] Thus, even the "eunuchoidal Klinefelters" may have a normal skeletal age, though some are retarded. Laboratory results usually indicate that excretion of urinary gonadotropin is increased, whereas plasma testosterone levels are generally in the low normal range, or even lower.[35]

Gonadal Aplasia

The short stature of Turner's syndrome (gonadal aplasia) is invariably present in XO individuals, and this has usually been attributed to a genetic factor.[4,21,25,28] Skeletal maturation is normal or only slightly delayed in childhood, but the delay increases in adolescence.[25,35] Acheson and Zampa[2] found that the majority show arrest in skeletal maturation.

Miscellaneous

In familial osteochrondrodystrophy (Morquio's syndrome*) and some of the chondrodysplasias, whole groups of centers may fail to appear,[13] and in epiphyseal dysostosis*, epiphyseal centers are often delayed.[32]

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*See page 1880.

When there is a deficiency of gonadal hormones, steroidal substitution therapy has been used successfully in many of these patients.[4,24,34]

Discussion

The determination in childhood of skeletal maturation relative to chronological age is well accepted. Standards offer a broad range of normal since the curves are rather flat and smooth. This is because the healthy population in the United States is made of heterogeneous individuals who differ widely in color, race, constitution and development. The great variability in the curves has prompted many radiologists to favor a multipart approach in maturation determination, assuming that the entire body must reveal more than just a single part.

Garn, Rohmann and Silverman demonstrated that selected centers of the hand, the foot and the knee contribute the most objective information on skeletal development during the first ten years of life. Many factors influence this development. Chromosomal effect is manifest very early. It is known for example that the male is retarded relative to the female, and the action of the Y chromosome probably begins at about seven intra-uterine weeks. Growth hormone and thyroid influence appear to have their greatest effect on centers which develop during infancy and childhood.

Garn, Rohmann and Silverman have stated that in puberty more attention must be given to centers of the hip and sesamoids of the thumb and other fingers. The present case revealed the iliac crest epiphysis as the only radiologically important finding and illustrates the relationship of this epiphysis to abnormal gonadal development occurring in an otherwise normal male (XY).

It was established by Elgenmark that in infancy, height shows a stronger correlation with ossification center development than age does; while later on, the correlation is largely equal. One might speculate in considering the eunuchoid habitus, whether the ossification of certain "androgen-dependent epiphyses" would not correlate equally with age and height.

The value of information on skeletal development must be weighed against the radiation cost, since radiographs of the hip may contribute to gonadal radiation. Pelvis roentgenograms should not be routine.

Since a delay in ossification and closure may radiographically reflect gonadal insufficiency, early closure may thus be used as an indicator of precocious puberty. When ossification or closure of the iliac crest epiphysis exceeds the normal range, it should be suspected that gonadal dysfunction is present. Other radiographic findings will help differentiate genetic dyscrasia from endocrine dyscrinism, and specific laboratory data now available will aid in establishing the definitive diagnosis.

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*See Test Your Word Score Page 1921.

Reprint request send to D. E. Dietrich, Maui Memorial Hospital, Wailuku, Maui, Hawaii.

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13-35. May be secured from the author or the reprints.

Thou shalt not kill; but need not strive officiously to keep alive.—Clough

A Patriarch's Ordeal

Poor Job! None the less to be commiserated with whether his afflictions were malevolent visitations or psychosomatic manifestations of utter despair!

A catalogue of his woes is horrendous—not so much in severity as in obduracy. The milieu for his trial was set by two personal calamities: first, his oxen, asses and camels were caused to be stolen (the word "caused" is here used advisedly); and second, his servants and sons were killed off. At this nadir of destitution and bereavement Job's harrowing physical and psychical ordeal began.

First came boils! One boil would be bad enough, but Job was literally covered "from the sole of his foot unto his crown." With no doctor at hand, he dealt with the boils himself by scraping them with a potsherd* a procedure that hardly sounds therapeutic and must have aggravated rather than alleviated the acute discomfort.

Following the boils came hallucinations: "Then a spirit passed before my face; the hair of my flesh stood up: It stood still, but I could not discern the form thereof: an image was before mine eyes."

Then insomnia and nightmares ensued: "I am full of tossings to and fro unto the dawning of the day. Then thou scarest me with dreams."

These were succeeded by more skin disorders: "My flesh is clothed with worms; my skin is broken and become loathsome."

Then, as if he had not undergone sufficient suffering and humiliation, his wounds were exacerbated and he had trouble breathing: "For he breaketh me with a tempest, and multiplieth my wounds without cause. He will not suffer me to take my breath."

Next, to add insult to injury, he developed wrinkles: "And thou hast filled me with wrinkles, which is a witness against me: and my leanness rising up in me beareth witness to my face."

A sequence of shocking assaults next descended upon him: "He hath broken me asunder: he hath also taken me by the neck, and shaken me to pieces, and set me up for his mark. He cleaveth my reins asunder, and doth not spare; he poureth out my gall upon the ground. He breaketh me with breach upon breach, he runneth upon me like a giant."

The sense of frustration, alienation and repudiation that resulted from his relentless persecution was abysmal! "But now they that are younger than I have me in derision. They abhor me, they flee far from me, and spare not to spit in my face."

But what appeared to be the proverbial "last straw" still did not end Job's appalling endurance test. He had yet to undergo one final shattering assault: "My bones are pierced in me in the night season: and my sinews take no rest. By the great force of my disease is my garment changed: it bindeth me about as the collar of my coat. He hath cast me into the mire, and I am become like dust and ashes. My bowels boiled and rested not. My skin is black upon me, and my bones are burned with heat."

Editor's Note: Diagnosis will be welcome.

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*See Test Your Word Score Page 1921.

Realism

The optimist says, "Please pass the cream."
The pessimist says, "Please pass the milk."
The realist says: "Please pass the pitcher."

Maxwell Droke: The Speaker's Handbook of Humor.

Primary Malignant Lymphoma of Small Intestine

Results of Treatment

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ALTHOUGH PRIMARY malignant tumors of the small intestine are uncommon, malignant lymphomas comprise up to 40% of such lesions.[1] In a review of the literature Cornes[2] stated that most patients with primary lymphoma involving the small intestine die within two years of the time of diagnosis or the beginning of treatment. Usher and Dixon's[3] statistics agree in that they had no survivors beyond two years in their 19 cases of jejunal and ileal lymphoma, the average survival being 5.8 months from the time of operation. Warren and Littlefield[4] reported the cases of two patients with duodenal lymphomas who underwent gastroenterostomy and postoperative irradiation and survived five and seven years, respectively. For some unknown reason, long survivals, irrespective of the degree of involvement or type of treatment, can be expected in 2 to 3% of all cases.[5]

Marcuse and Stout[6] reported 20 five-year survivors (13.3%) among 150 patients with lymphoma of the small bowel treated by diverse means. "They were unable to determine any correlation between the clinical and pathologic aspects and the final outcome. Some patients with advanced lesions recovered, while others with early lesions suffered rapid progression of the disease despite radical therapy. The presence of involved nodes did not always preclude a successful outcome. . . ."[6]

Stout[7] considered two criteria useful in predicting survival: the cell type and the patient's age at onset of disease, the prognosis for five-year survival being better if the onset occurred after 40 years of age. (He had no 10-year survivors among the patients whose disease began in the first three decades of life.) With respect to cell type, most investigators agreed with his contention.

It is not possible on the basis of histologic type to predict the tumor's propensity to spread. However, certain generalizations based on statistics have been made, including the one that giant follicular lymphoma tends to remain localized for many years. Stout[7] reported an augmented survival of 12% for his patients with gastrointestinal lymphomas of this type. Reticulum cell sarcoma, Hodgkin's sarcoma, and lymphoblastic lymphoma, by contrast, usually spread fairly rapidly.[2] Stobbe and coworkers[8] reported a much worse outlook for patients with reticulum cell sarcoma than for lymphoblastic lymphoma and Hodgkin's disease of the stomach.

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*Mayo Clinic and Mayo Foundation: Section of Therapeutic Radiology.

†Mayo Clinic and Mayo Foundation: Section of Surgical Pathology.

‡Mayo Clinic and Mayo Foundation: Section of Surgery.

Concerning treatment, a program combining surgical resection of the involved intestinal segment with postoperative irradiation has offered the best prognosis in cases of localized lymphoma. However, long-term survivors have been reported after the use of either modality alone, as has been the case with occasional spontaneous regression, without therapy, of histologically verified lesions.

Present Study

The cases of 44 patients with primary malignant lymphoma of the small intestine who were seen at the Mayo Clinic during the 12-year period from January 1, 1951, to December 31, 1962, were reviewed, and surgical specimens, when available, were examined. If doubt existed concerning the primary site of the disease process in the small intestine, the case was eliminated from this study. Survival data were calculated to December 1, 1968.

Microscopic sections made in each case were reviewed by one surgical pathologist to ensure uniformity in the histologic classification.

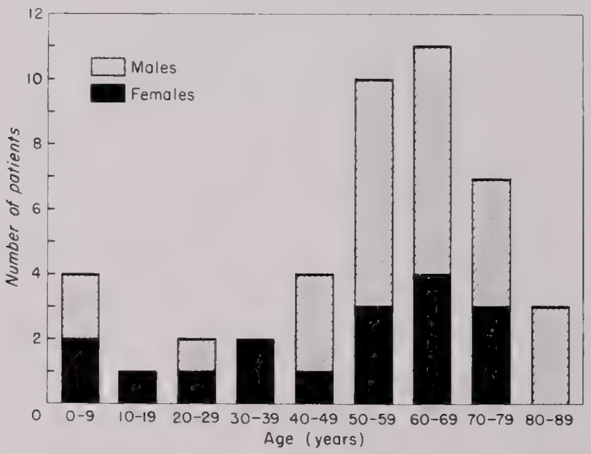

Fig. 1—Age distribution of the 44 patients at time of diagnosis.

Available roentgenograms were reviewed in conjunction with the specimens and the original surgical reports in an attempt to correlate distinctive anatomic and roentgenographic findings. No roentgenographic criteria diagnostic of lymphoma primary in the small intestine were discovered. On the contrary, the characteristic roentgenologic appearances previously ascribed to other diseases of the small bowel, both neoplastic and non-neoplastic, were demonstrated in cases of lymphoma verified by tissue examination.

Clinical Aspects

The group under study included 27 males and 17 females, forming a ratio of males:females of 1.6. The youngest patient was two years old, the oldest, 88. Figure 1 shows the age distribution by sex of the 44 patients at the time of diagnosis.

Clinical symptoms and signs were not diagnostic. Predominant presenting symptoms were abdominal pain and loss of weight. An increase in the amount of weight lost did not correlate directly with increased duration of symptoms. A palpable abdominal mass was the most frequent sign found on physical examination. Other than elevation of the sedimentation rate, results of other laboratory examinations were not contributory.

Treatment

All patients underwent surgical exploration (Table 1). Resection was carried out in 38 and biopsy with or without some bypass procedure in six. The surgical specimens were reviewed, and the length of the lesion was noted and classified into one of three groups according to Table 2. Seven patients had resection alone as the definitive treatment, whereas 31 had roentgen therapy after operation. In six of the 44 patients, the disease process was too extensive for resection. Biopsy with subsequent enterostomy, bypassing the lesion, was performed on four patients, each of whom received roentgen therapy in the postoperative period. One patient had biopsy alone followed by irradiation. One patient died during the postoperative period after biopsy and enterostomy and, therefore, did not receive roentgen therapy. In all, five patients died within one month after operation.

Pathologic Features

Classification

Dockerty's modification of Dukes' classification was applied to the tumors (Figure 2). In this classification, Type-A lesions involve only the mucosal layer of the bowel. None of the lymphomas in the present group were so limited. Sixteen lesions were classified as Type B: that is, deep mural invasion existed and occasionally extended to the peritoneum. Metastasis to regional nodes, Type C, was demonstrated in 26 cases. The latter group, comprising 62%, included the six cases of extension of tumor beyond the small bowel in which biopsy alone was performed. Insufficient information existed for classification of the remaining two of the 44 cases.

Gross Aspects

Most of the lesions were ulcerating, with the larger growths being annular. Almost a third of them were perforating. In 12 instances a peculiar appearance presented in the form of a cylindrical or aneurysmal dilatation of the bowel over the zone of lymphomatous involvement.

Microscopic Features

After review of the microscopic sections of the specimens, 20 lesions were classified as reticulum cell sarcoma, seven as lesions typical of Hodgkin's disease, eight as lymphoblastic

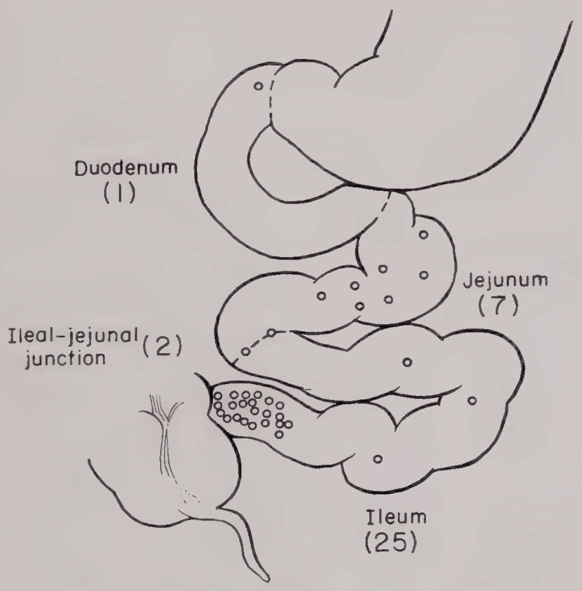

Fig. 3. Primary sites of 35 solitary lesions.

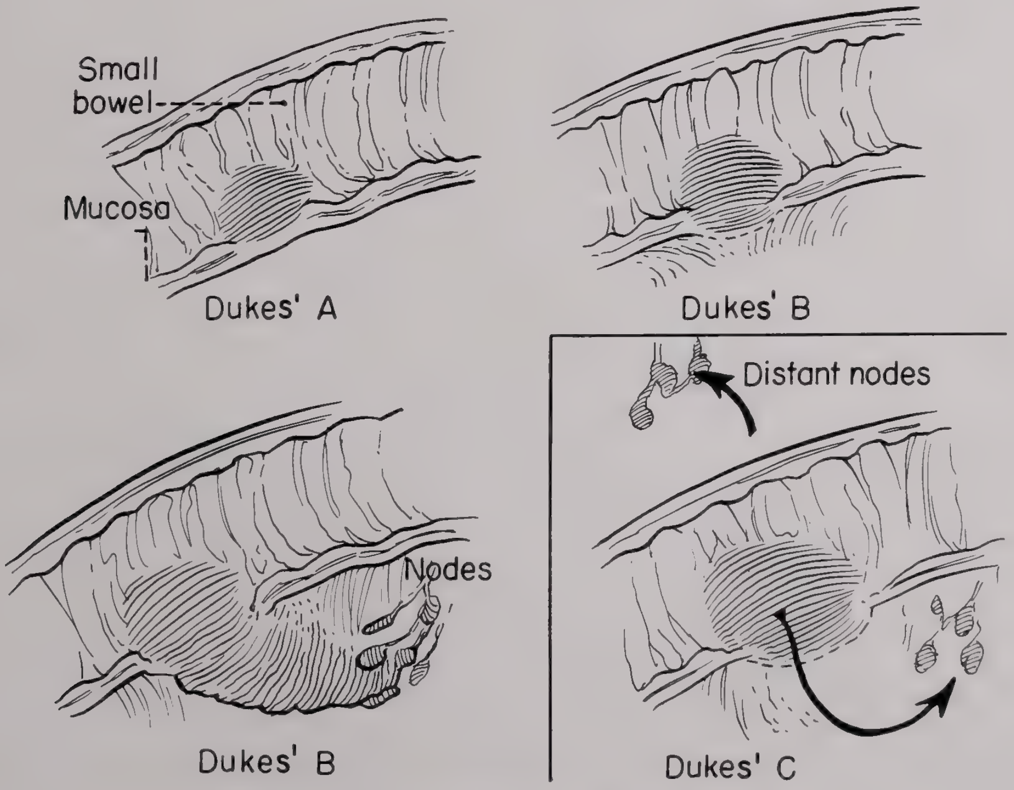

Fig. 2—Dockerty's modification of Duke's classification.

lymphoma, six as lymphocytic lymphoma, and three as giant follicular lymphoma. In 35* of the 44 patients involvement was unicentric, with 25 having tumors primary in the ileum. Two patients had lesions involving the small bowel at the ileo-jejunal junction, seven had primary jejunal lymphoma, and one patient had primary duodenal lymphoma (Figure 3).

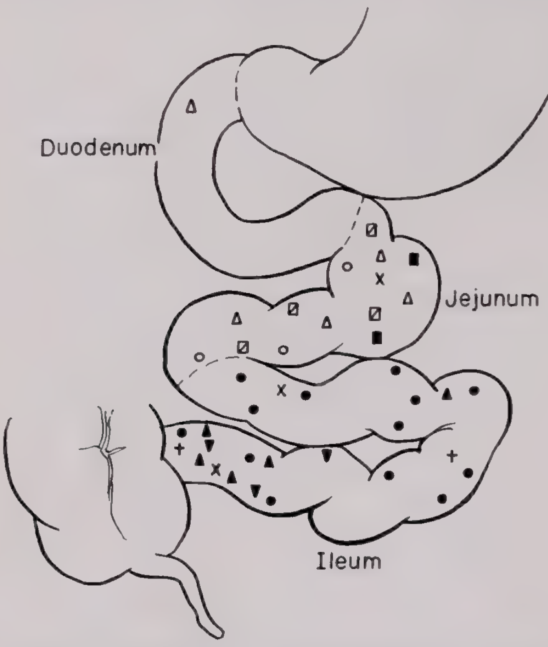

Fig. 4—Primary sites of multiple lesions in nine patients.

The remaining nine (20%) of the 44 patients had multiple sites of involvement within the small bowel. The jejunum alone was multicentrically involved in three patients and the ileum alone in four. The jejunum and ileum were both involved in one patient. Another patient had a solitary duodenal lesion with four lesions in the jejunum (Figure 4).

No relationship was found between cell type and location of the lesion in the small bowel, or between cell type and involvement, that is, whether sites were solitary or multiple.

Results

All of the 44 patients were eligible for five-year follow-up studies (Table 1). Fourteen (32%) survived five years or more. If the five patients who died during the immediate postoperative period had been excluded, the five-year survival rate would have been 36%. The five-year survival for the 31 patients who had both resection and irradiation was 45%.

Survival

Five-year survival according to treatment is listed in Table 1. The location of the primary lesion within the small bowel did not appear to affect survival (Figures 5 and 6), nor was survival statistically related to the sex of the patient (Figure 7). As would be expected, those with less extensive lesions, that is, lesions classified as Dukes' Type B, had a better chance of survival (50%) (Table 3) than those with

TABLE 1

Treatment

Treatment	Follow-up 5 years after operation: Living	Follow-up 5 years after operation: Dead
Surgical resection		
With roentgen therapy	14	17
Alone	—	7*
Biopsy		
With roentgen therapy	—	1†
With bypass enterostomy	—	1†
With bypass enterostomy and roentgen therapy	—	4
Total	14	30

*Includes three postoperative deaths (one was cardiac arrest at operation). Terminal date of survival and studies was December 1, 1968.

†Postoperative death (that is, death within one month of operation).

TABLE 2

Classification of Specimens by Length of Lesion

Longitudinal measurement of lesion, cm	Number of cases*
<5	9
5 to 10	29
>10	11

*The total number of cases is greater than 38 because of multiple sites of involvement.

TABLE 3

Modified Dukes' Classification

Classification	Follow-up 5 years after operation: Living	Follow-up 5 years after operation: Dead
Dukes' Type A	—	—
Dukes' Type B	8	8
Dukes' Type C	6	20
Indeterminate from information	—	2
Total	14	30

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*In six cases in which biopsy alone was done, the site of tumor stated in the surgical report was accepted.

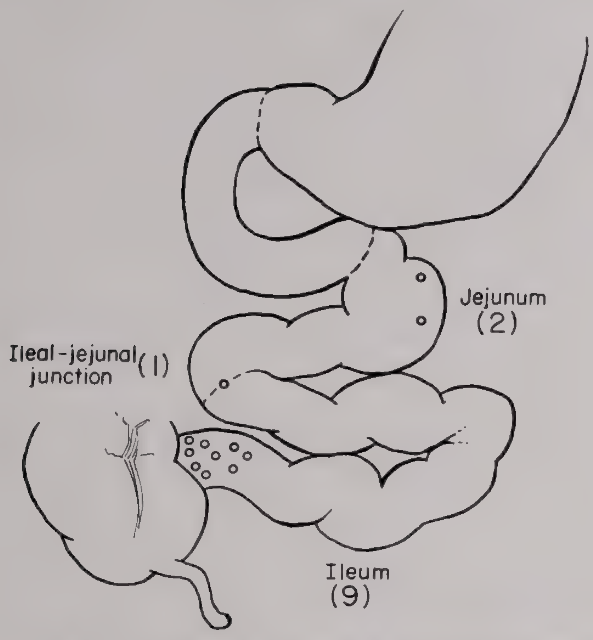

Fig. 5—Primary sites of lesions in five-year survivors with solitary lesions.

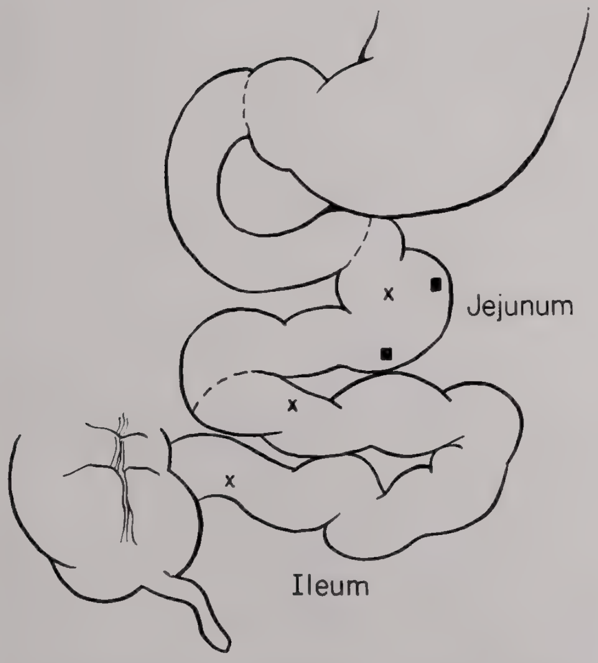

Fig. 6—Primary sites of lesions in five-year survivors with multiple lesions.

Dukes' Type C lesions.

As far as Stout's[7] contention that cell type has a bearing on survival, five of 20 patients with reticulum cell sarcoma were living five years after operation; three of six patients with lymphocytic lymphoma survived a similar period (Table 4).

TABLE 4
Microscopic Diagnosis

Diagnosis	Follow-up 5 years after operation	
	Living	Dead
Reticulum cell sarcoma	5	15
Lymphoblastic lymphoma	2	6
Lymphocytic lymphoma	3	3
Hodgkin's disease	2	5
Giant follicular lymphoma	2	1
Total	14	30

Only one of seven patients with disease presenting in the first three decades of life survived five years or more (Figure 7).

The surgeon's notes were interesting. Of the 14 survivors, seven were believed to have had all of the grossly involved portion of the small intestine surgically removed, while of the 30 patients who died within five years, only three were considered to have had all diseased intestine surgically resected.

The reasons that seven patients did not receive roentgen therapy after operation were as follows: Four died before such therapy could be started (three within the 30 days immediately after operation and another six weeks after operation). One patient, 79 years of age with a fractured hip, was considered too elderly to undergo the rigors of roentgen therapy. Another elderly man had had such extensive resection and had such persistent diarrhea that he was not considered a satisfactory candidate for roentgen therapy. In one case roentgen therapy was denied because of the surgeon's impression that the patient had no residual tumor.

Dosimetry

Records of roentgen therapy received by these patients were reviewed and dosimetry* was approximated by using the Alderson phantom.

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*See Test Your Word Score Page 1921.

In the early part of this study, supervoltage equipment was not available, while in the group treated from the late 1950s onward, cobalt teletherapy was often employed. In the patients who survived five years, selected treatment plans were re-created, using the Alderson phantom. Field sizes recorded in the patient's record of roentgen therapy and treatment factors were duplicated.

Roentgen therapy was begun two weeks to one month after operation, depending on the patient's clinical condition. Generous fields were employed in most instances with opposing portals used to irradiate the abdomen from the dome of the diaphragm to the inferior margin of the symphysis pubis. Prior to initiating therapy, careful physical examination did not demonstrate peripheral adenopathy. Neither the liver nor the spleen could be palpated in any instance. Tests of liver function performed prior to operation did not reveal any abnormality. Roentgenograms of the chest showed no evidence of mediastinal adenopathy or parenchymal lesions.

In every case in which a gross residual tumor remained after operation and in which five-year survival was achieved, the patient had received a minimal dose of 2,000 rads at the level of the midplane of the abdomen. Fractionation varied from 16 to 20 days of treatment, as indicated in the following report.

Case Report

History

In December 1955 a 71-year-old man was hospitalized because of vomiting of two weeks' duration. In 1953 he had experienced a sudden hemorrhage from the rectum. A burning sensation in the abdomen, noted the night before, was followed by passage of bright red blood at 5 a.m. At that time transfusion of blood was required. On November 28, 1954, he had a sudden single episode of severe hematemesis which ceased after transfusion of blood and emergency treatment including gelfoam liquid. The last hemorrhage from the rectum took place on May 5, 1955, at which time the patient stated that he had had an attack of influenza approximately one week earlier. He took a laxative, after which he had diarrhea soon followed by bleeding. On May 13, 1955, he received a blood transfusion. In June 1955 the patient was examined at the Mayo Clinic. At that time no cause for his gastrointestinal symptoms could be found.

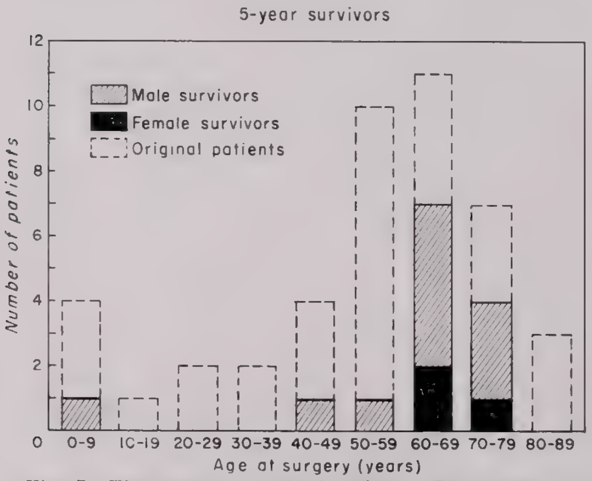

Fig. 7—Five-year survival of patients. Distribution by age at operation and by sex.

Two weeks prior to his hospitalization in December 1955 the patient began to vomit after eating. Vomiting relieved the pressure and made him feel better. In the morning he felt well; however, as the day progressed he noted increasing discomfort in the upper part of the abdomen. He felt that his food was being retained too long and stated that "when the next meal comes it accumulates." During the night, when he did not eat, the abdominal discomfort decreased. Bowel habits continued to be normal until two days prior to his hospitalization. At that time he stopped eating solid food. His appetite, however, was good, but he had lost 24 pounds during the previous six months.

The patient was born and raised in Russia and came to the United States at the age of 21 years. In 1918 he had had a "severe" attack of influenza. In 1940 he had undergone a submucous resection and adenoidectomy elsewhere. In 1951 he noticed a left inguinal hernia but did not seek medical advice.

Laboratory Findings

Results of laboratory studies on December 2, 1955, were as follows: hemoglobin 13.8 gm with a leukocyte count of 6,600 and a differential of lymphocytes 21, monocytes 4, neutrophils (segmented 56, band form 18), and eosinophils 1. The erythrocyte count was 4,310,000. The blood urea was 54 mg/100 ml. Sodium was 137, potassium 4.0, chlorides 98, and Co_2 21 mEq/liter.

On December 6, 1955, after fluoroscopic examination of the upper gastrointestinal tract, the roentgenologist reported that loops of jejunum in the left upper quadrant were bound together and distended. The loops were difficult to examine, but he suspected that there was an enteroenteric fistula which was probably related to a malignant lesion in the jejunum.

Treatment

On December 10, 1955, the patient underwent operation through a primary left rectus incision. Above the stomach, apparently in the celiac axis region, were multiple enlarged, firm lymph nodes which could not be exposed. The proximal jejunum was dilated and a huge mass in the upper jejunum was surrounded by omentum and fat tags. Part of the omentum was removed. The fat tags were excised, which mobilized the lesion well. The mesentery contained many large nodes. As much as possible of the mesentery was removed without sacrificing the superior mesenteric artery, but many enlarged nodes remained. Wide resection was accomplished. A fistula between loops of jejunum was exactly as described by the roentgenologist. The entire mass came out cleanly and end-to-end jejunojejunostomy was established. The defect in the mesentery was closed by suture. No other lesions could be demonstrated.

The pathologist reported an annular, ulcerative, perforating, necrotic, obstructing reticulum cell sarcoma measuring 14 by 7 by 5 cm. It had produced a fistula into the jejunum 10 cm distal to the lower level of the primary tumor. The lymph nodes were inflamed. The lesion was classified Dukes' Type B.

On January 9, 1956, the patient began roentgen therapy. A cobalt-60 teletherapy unit was employed with a source-skin distance of 80 cm. Treatments were directed through opposing anterior and posterior portals measuring 16 by 15 cm and over 18 treatments 2,000 rads were delivered at the level of the midplane of the abdomen.

The patient was last examined at the Mayo Clinic on November 27, 1957, at which time there was no evidence of recurrent sarcoma. In a follow-up letter on October 26, 1966, the patient stated that he had high blood pressure but no known recurrence of his tumor.

Summary

At the Mayo Clinic, 44 cases of primary malignant lymphoma of the small intestine were encountered during the 12-year period, January 1, 1951, to December 31, 1962. Cases were reviewed and surgical specimens, when available, were examined. If doubt existed concerning the primary site of the disease process in the small intestine, the case was eliminated from the study. Survival data were calculated to December 1, 1968. All patients had undergone surgical exploration. Records of roentgen therapy of these patients were reviewed and dosimetry was approximated by measurements using the Alderson phantom. The current treatment of choice for primary malignant lymphoma in the small bowel is surgical resection followed by roentgen therapy. No five-year survivors in this group were obtained by any other method of treatment.

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Robert C. Knutson, M.D.

This cover was reproduced from a watercolor painting by Dr. Robert C. Knutson, St. Paul anesthesiologist.

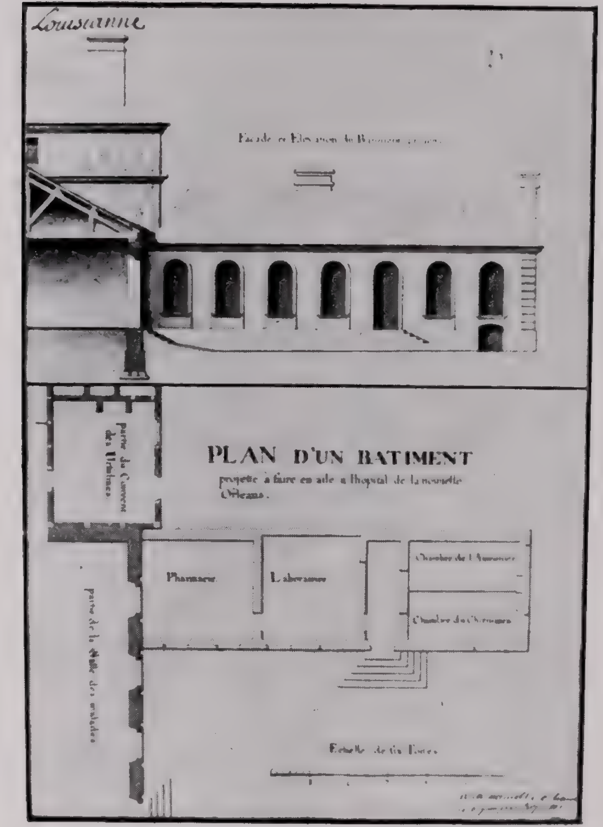
"Frosty Morning" was sketched from nature on Old German Road in Dakota County, Minnesota, and then finished inside—it was ten below zero! The effect of frost on trees was obtained by scratching off paint with the point of a scalpel blade, allowing the white of watercolor paper to show.

Doctor Knutson has received prizes for watercolors in The Twin Cities Artists' Exhibit at the Minneapolis Institute of Arts and in the art exhibit of the Minnesota State Medical Association.

The world is full of willing people; some willing to work, the rest willing to let them.—Robert Frost

Old Hospitals

The Royal Hospital of New Orleans


Louisianne
PLAN D'UN BATIMENT
projetté à faire en aile a l'hopital de la nouvelle Orleans.
partie du Convent des Ursulines
Pharmacie
Laboratoire
partie de la salle des malades
Echelle de six Toises

Broutins plan and elevation of a wing of the hospital, dated June 6, 1737. reference: Archives Nationales, section Outre-Mer, Atlas Moreau de Saint Mery, No. 28.

The first hospital in the Mississippi Valley was the military hospital built at the newly-founded French colonial city of New Orleans. Completed in 1722, it was a wood frame building, fifty by twenty feet, raised a foot or two off the ground, and located on the quay facing the river at the corner of the present Ursuline Street.

The tiny facility was designed to accommodate sixty to eighty patients. Situation of the new city in the midst of fever-ridden swamps, however, soon resulted in an influx of the sick which overflowed the hospital and forced the use of an uncompleted warehouse for convalescents.

By 1726, a companion building the same size as the first had been completed, allowing separation of patients with infectious diseases from the others. The hospital grounds were surrounded by palisades enclosing gardens to provide fresh vegetables for the sick. In the same year, the Ursuline nuns of Rouen in France agreed to undertake the task of caring for the patients of the New Orleans hospital.

A convent for the Ursulines was begun about a block downstream from the hospital. The hospital buildings were deteriorating so rapidly that the colonists decided to relocate the hospital adjacent to the new convent on what came to be called Hospital Street, now Governor Nicholls Street. In August, 1732, one of the old hospital buildings was destroyed by a hurricane, crushing 26 beds and accompanying furniture. Fortunately, the patients had been removed before the structure collapsed.

(Continued to page 1921.)

Regional Enteritis

Early Diagnosis

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My purpose in writing on the subject of regional enteritis is to emphasize those features which might enable us to make the diagnosis much earlier in the course of its clinical evolution. These features include both clinical and radiological considerations.

Early Clinical Considerations

Perhaps ten percent of cases appear as acute abdominal emergencies. If there is no clinical clue that one might be dealing with a more chronic disease, the patient is often operated on with a tentative diagnosis of appendicitis. After seeing the tremendously thickened discolored ileum, the surgeon will usually recognize his error, realizing that many of these lesions, especially in children, regress spontaneously. Accordingly, most surgeons will close the abdomen without bowel resection or anastomosis. Even in the cases where the diagnosis is suspected at surgical exploration, the surgeon is well advised to confirm the diagnosis and determine the extent of the disease roentgenographically. The clinician must order a barium enema and indicate his suspicions in order that the radiologist can carry out the proper technique to make the diagnosis on the basis of these studies. These two requirements seem simple enough but, due to the failure of one or the other, the diagnosis is frequently delayed for months and years. In reviewing the charts of many of these patients, it is remarkable how frequently the patient has carried a diagnosis of psychosomatic disease until a diagnosis of regional enteritis was eventually established.

If one waits for the classical clinical history of fever of undetermined origin, intermittent abdominal cramps and diarrhea, extensive weight loss, abdominal gurgling, and all of the other signs of debilitating disease before thinking of regional enteritis, he will almost always diagnose it in an advanced stage. In the modern practice of medicine, this diagnosis should be made whenever there is a suspicion of disease of the gastrointestinal tract. Obviously, anyone with an externally draining fistula or pararectal abscess, in view of the frequent association with ileitis or ulcerative colitis, should be studied.

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Roentgen Diagnosis

Once the roentgen examinations are ordered the diagnostic burden is on the radiologist. This observer has been impressed by the number of these patients who have had what was called a normal barium enema previously. Most of these people did not have a small bowel study. Roentgenograms from a few of these outside studies were reviewed; most of them were non-diagnostic technically.

Why does a radiologist miss the diagnosis of regional enteritis? It cannot be that he has not heard of the "string sign" and the "skip areas." The radiologist must establish a routine of seeing the terminal ileum in every examination in which it is possible to fill it.

Adequate Filling

It is distinctly unusual not to be able to fill the ileum when the ileocecal valve is infiltrated by the inflammatory process of regional enteritis. When the ileum is filled in good volume, sharp spot films should be made of the area. If there is the slightest suspicion of mucosal irregularity on the enema study, a small bowel should be done with 24 ounces of a non-flocculating barium. In this way the entire small bowel can be filled in continuity, and thus the study proceeds much more quickly. When the entire small bowel is filled, an abnormally thick-walled loop is easily recognized by virtue of displacement of adjacent loops of bowel. With the non-flocculating barium the mucosal pattern is exquisitely outlined.

Serial Roentgenograms

A series of roentgenograms is made beginning at five minutes after completion of the upper gastrointestinal study. From then on the timing is based on the rate of progress. It is important to see all areas of the small bowel more than once. Transitory configurations often stimulate pathology, but if the pattern is truly abnormal, it will be persistent. The terminal ileum should be seen clearly emptying into the ascending colon on more than one film. This is by far the most important portion of the small bowel since it is the most frequently involved in disease processes. This includes adhesions, periappendiceal abscesses, lymphosarcoma, and carcinoma of the cecum, in addition to regional enteritis.

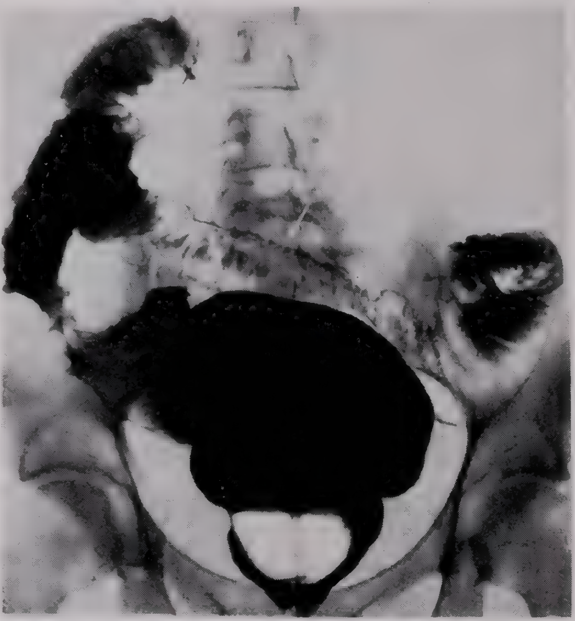


Fig. 1A—Patient has had a previous colectomy with ileosigmoid colostomy. There is narrowing at the anastomosis (single arrow) which overlies the wing of the right ileum. The ileum above the anastomosis is slightly dilated. Its mucosal margin is etched (double arrow). There is diffuse ulceration of the distal 25 centimeters of the ileum.

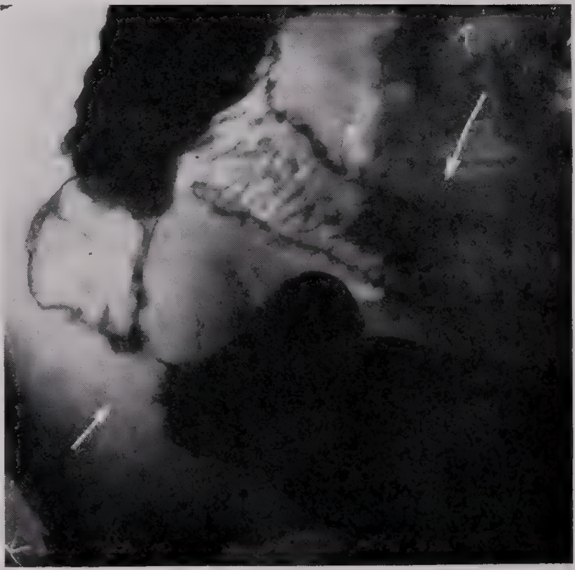


Fig. 1B—Spot film of the anastomotic (single arrow) area demonstrates more effectively the diffuse shaggy ulceration (double arrow) involving all of the visualized portion of the ileum to the level of the anastomosis. Changes are consistent with a diagnosis of regional enteritis.

Distortion of Mucosal Pattern

There is primarily one finding we must seek out. This is simply *any* constant distortion of the mucosal pattern. If all we see is a faintly fuzzy small bowel margin several centimeters in length on two or more films, we may be suspicious. If there is the slightest evidence of thickening of bowel wall along with it, we have enough evidence to make the diagnosis; any more advanced changes make the diagnosis more certain. Even in the early stages, the involved loops maintain a fixed position that is very helpful in ruling out a transient mucosal distortion.

Case Presentations

Case 1

This 37-year-old white female presented in 1960 with many complaints. Her appetite was poor and she stated that she might have lost some weight. She complained also of mild abdominal gurgling. In retrospect, it was clear that she had had symptoms for at least three years prior to her workup in 1960, which was done because of the presence of anemia. She had had a colectomy for chronic ulcerative colitis in 1951, when the terminal ileum was anastomosed to the sigmoid. Subsequently she had had no gastrointestinal symptoms until 1957 when her present gastrointestinal symptoms began. A barium enema, upper GI study, x-rays, and sigmoidoscopy at a University center revealed no abnormality. Because of this negative result no further definitive examination was made until 1960 when a sigmoidoscopy examination was again done. Diseased bowel was seen proximal to the anastomosis. A barium enema showed evidence of a previous colectomy with ileosigmoidostomy (Figure 1). The stoma was appreciably narrowed. The more proximal ileum was moderately dilated. There were approximately 25 centimeters of terminal ileum involved with a diffuse ulcerative process.

Comment

In this patient there was a three-year delay in recognition of acute disease despite the fact that she had had a previous colectomy for chronic ulcerative colitis. Pertinent also is the fact that she had had a negative gastrointestinal workup in 1957, but without a small bowel study.

Case 2

This 27-year-old female, after delivery of a child in 1953, complained of recurrent diarrhea with three to five bowel movements daily and gave a history of having had an episode of diarrhea lasting several months in 1951, associated with gaseousness and gurgling abdominal sounds. On examination active bowel sounds were noted. An initial barium enema, at this clinic in 1953 (Figure 2-A, B), was called normal despite the large

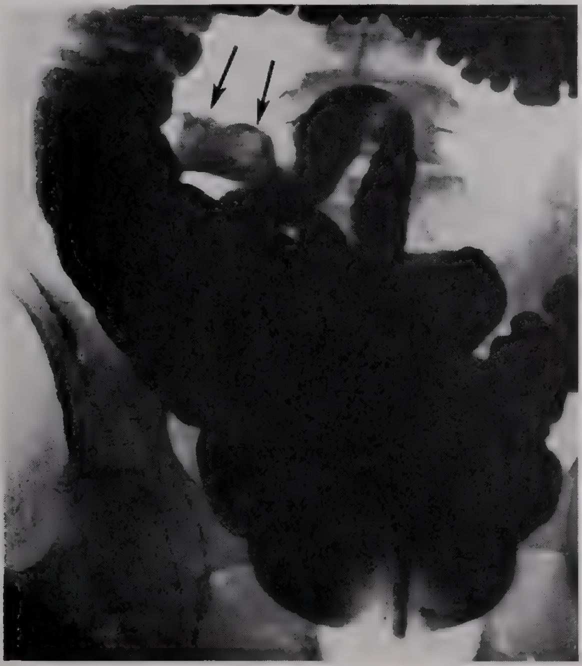


Fig. 2A—Filled film on barium enema dated March 21, 1953. There is mottled radiolucency in the right colon representing retained fecal material. Filling defects (arrows) in the ileum were assumed to be on the same basis. Note irregular and fuzzy contour of the terminal ileum. There is separation of ileal loops.

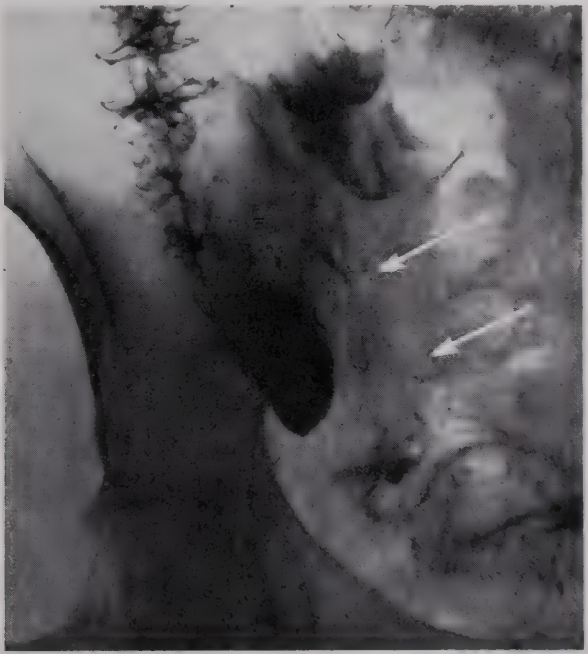


Fig. 2B—Postevacuation barium enema March 21, 1953. The evacuated ileum (arrows) does not have a normal feathery mucosal pattern. The ileum lying within the right side of the pelvis has a denuded appearance highly suggestive of regional ileitis. The diagnosis should have been made at this time.

amount of retained fecal material within its ascending segment and also in the terminal ileum. Serration of its wall was regarded as of no significance. No small bowel study was ordered.

In 1963, ten years after the original one, the patient had a second barium enema here which showed extensive regional enteritis (Figures 2-C, D).

Comment

It is clear that the serration of the ileum seen on the initial study was a significant finding. We can learn from this case not to dismiss minimal mucosal findings. A small bowel study should have been done in 1953. A barium enema should have been repeated, with an attempt at better bowel preparation.

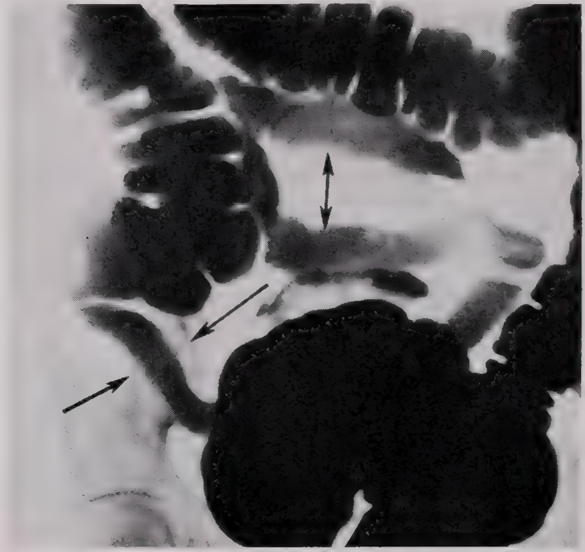


Fig. 2C—Followup barium enema March 16, 1963. This study, including pre-and post-evacuation roentgenograms, shows the extensive changes of regional enteritis. There has been progression since earlier study of 1953 (arrows).

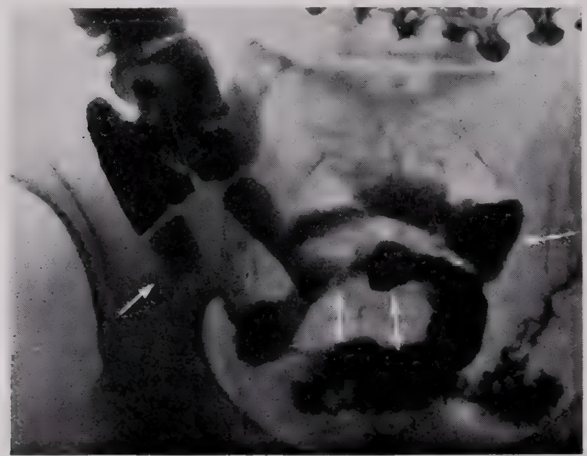


Fig. 2D—Extensive changes of regional enteritis.

Case 3

This 34-year-old white male was first seen on November 15, 1958, and was treated initially for functional bowel complaints including intermittent diarrhea. He complained also of intermittent distress in the right groin area. He was checked for a hernia but none was found. He returned in March of 1959, at which time a partial workup was normal. In September of 1959 he complained of recurrent pain in the right lower quadrant and groin. In March of 1963 he returned with recent onset of diarrhea. At this time both the barium enema and small bowel studies showed typical but mild changes of regional enteritis (Figure 3).

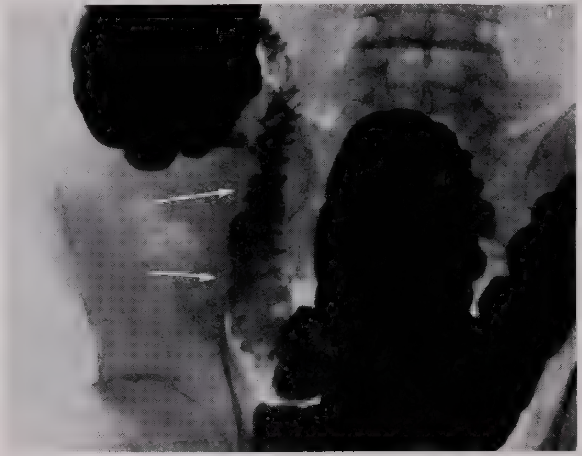


Fig. 3A—Barium enema with filling of terminal ileum. There are numerous "cobblestone" filling defects (arrows) within the terminal ileum. There is slight marginal irregularity of the ileum. On the basis of this film alone, it would be difficult to be certain that we are dealing with regional enteritis. A similar appearance could be given in the presence of prominent lymphoid follicles.

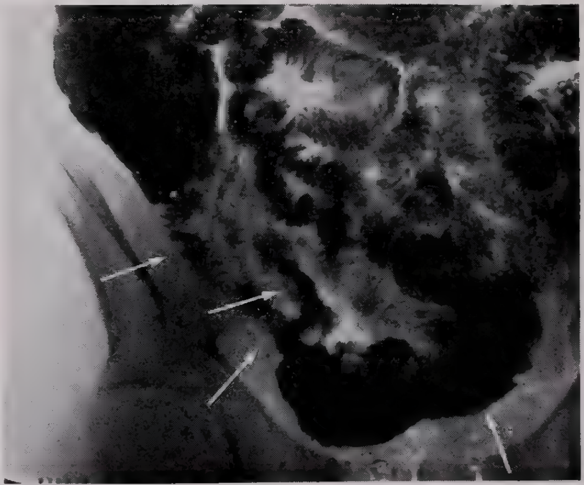


Fig. 3B—Roentgenograms of a small bowel series done three days after the barium enema. We see numerous abnormal small bowel loops (arrows). There is separation of the loops due to the thickened walls and pointing of circular small bowel folds with irregularity of the pattern of the folds. These are minor but constant changes and clearly indicate the presence of regional enteritis.

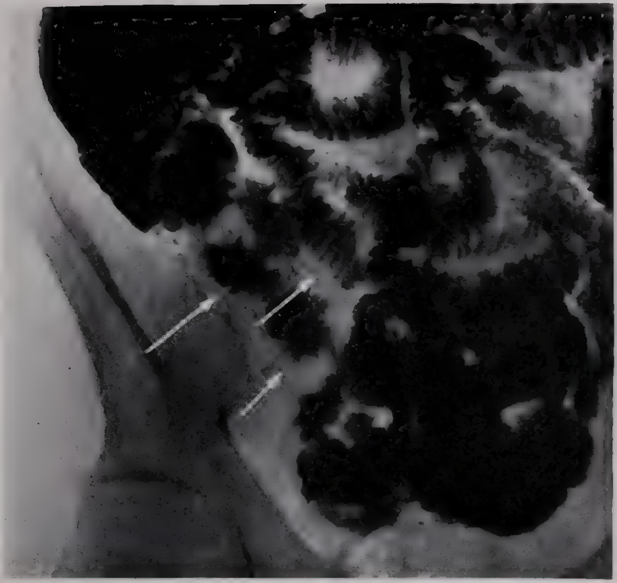


Fig. 3C—Roentgenogram of small bowel series done three days after the barium enema.

Comment

This man was treated on an assumption of functional bowel complaints. He went almost five years before having either a barium enema or a small bowel study.

Case 4

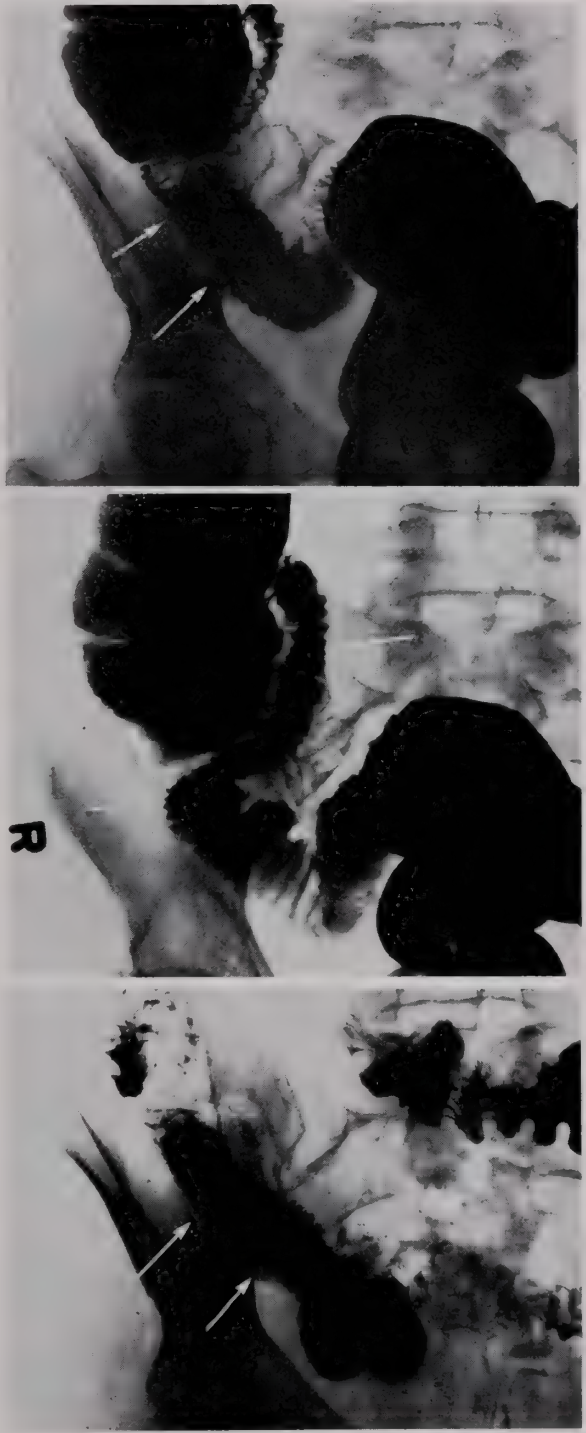
This 33-year-old female complained of chronic abdominal distress and indigestion in January 1957. She had belching relieved by Alka-seltzer. There was mild abdominal tenderness localized directly over the umbilicus. An upper gastrointestinal x-ray was called normal. She returned in March of 1958 because of chronic intermittent bowel complaints manifested by three to four bowel movements daily and a feeling of gaseousness. On physical examination her abdomen was negative. The tentative diagnosis was chronic irritable bowel syndrome. She was seen again in April and May for persisting gastrointestinal symptoms associated with diarrhea, cramps and gurgling. Physical examination revealed hyperactive bowel sounds. A barium enema, done on May 20, 1958, showed minimal changes of terminal ileitis (Figure 4).

Comment

There was a delay from onset of symptoms to definitive gastrointestinal tract workup of one and a half years. Again noted is the functional diagnosis of "chronic irritable bowel syndrome."

Case 5

This 38-year-old male appeared in 1965 complaining of severe diarrhea, with five to six bowel movements daily which were relieved by large doses of paregoric.



Figures 4A (top), B (middle), and C (bottom)—Barium enema. Prone, supine, and postevacuation roentgenograms of the right lower quadrant demonstrate a fixed position of the distal ileum relative to the colon and to the surrounding bony structures. The margin of the terminal ileum is somewhat fuzzy (arrows). There is a slight loss in the normal orderly pattern of the circular folds. From the standpoint of the roentgen diagnosis, the findings are considered highly suspicious of regional enteritis. The diagnosis is, however, not unequivocal. A small bowel study was suggested, but the patient was lost to followup.

He was hospitalized one month later for this same complaint. A barium enema and upper gastrointestinal and small bowel x-ray studies were called normal. The patient was told that his problems were probably psychiatric in nature. Despite this he continued to have diarrhea. While on a business trip in August 1965 he noted abdominal pain and distention. Admitted to a hospital he was given intravenous fluids as well as antibiotics. Apparently at that time he had had no bowel movement as his symptoms were relieved when his bowel movements began, and he was told that he had had an episode of acute bowel obstruction. When he returned to this city he again began to have intermittent bowel complaints, and on this occasion he had another gastrointestinal workup. The barium enema showed regional ileitis involving the terminal 20 centimeters of ileum. This was confirmed by a small bowel study (Figure 5). The patient has responded well to therapy with corticosteroids, antibiotics, and a general antidiarrhea regime. However, he flares up frequently when weaned off drugs or with any dietary indiscretion.

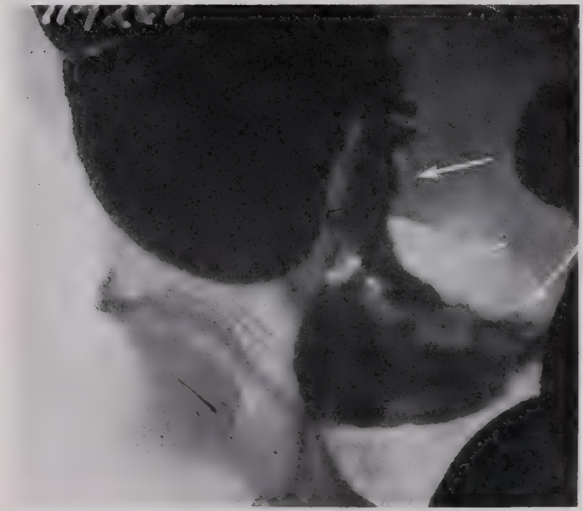


Fig. 5A—Spot films of the terminal ileum from a barium enema study. There is loss of mucous membrane pattern (arrows) and irregularity of the lumen of the ileum. There are filling defects and presumably ulcerations of the ileum.

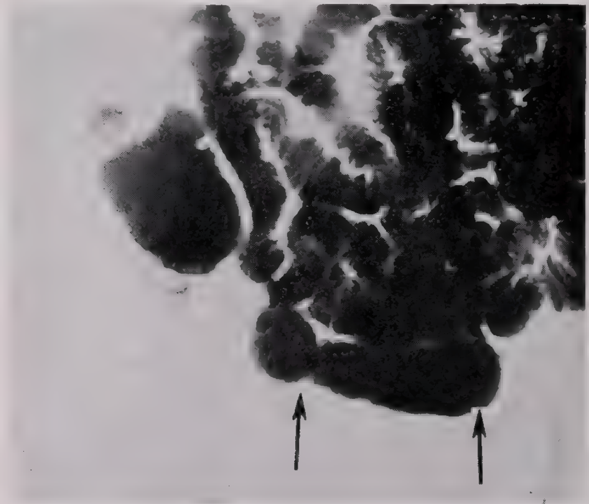


Fig. 5C—Small bowel study does not demonstrate the area of involvement very effectively. The very lowest small bowel loop demonstrated is, however, clearly abnormal (arrows).

Comment

This patient had severe complaints. He was clearly a tense and jittery individual, and this was undoubtedly aggravated by the fact that no organic disease could be found to explain his symptoms. He improved considerably with the simple knowledge that he had a real disease of his bowel.

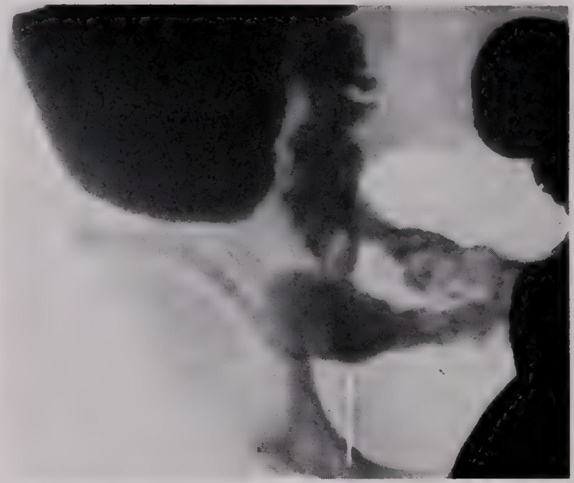


Fig. 5B—Spot film of the terminal ileum from a barium enema study.

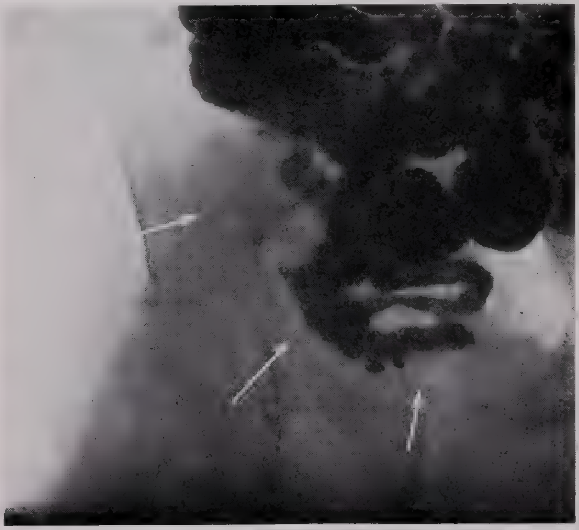


Fig. 6A—Roentgenograms from small bowel study show a constant pattern of denudation of mucosa, irregularity of lumen, fixation of position, and separation of adjacent loops (arrows). Findings are characteristic of regional enteritis.

Case 6

This 23-year-old white male was recognized as being anemic when he went to the blood bank to donate blood. His hemoglobin at this time was 10.4 grams. He stated that he was feeling fine. He was admitted to the hospital for a workup to determine the cause of his iron-deficiency anemia. Though a barium enema and upper gastrointestinal study were called normal, a subsequent small bowel study (Figure 6) showed involvement of the descending duodenum with narrowing and some loss of mucosal pattern in the mid-ileum characteristic of regional enteritis. In retrospect the patient recalled that he had had some diarrhea and cramps. About four months after the diagnosis was made he was having loose bowel movements and was then put on steroid therapy with an apparent good bowel response. This patient has left the city and we have no report relative to the response of his anemia.

Comment

The referring internist had elicited no history of gastrointestinal disturbance; hence we can only presume that the regional enteritis was the cause of his anemia. This case stresses the importance of seeing the terminal ileum and having good spot films of it.

Conclusion

A high index of suspicion by both the clinician and the radiologist can lead to the earlier diagnosis of regional enteritis.

Acknowledgment

Many thanks are due to Miss Monica Doran, Chief Technician, and other technicians at the St. Louis Park Medical Center for their help in assembling these cases.

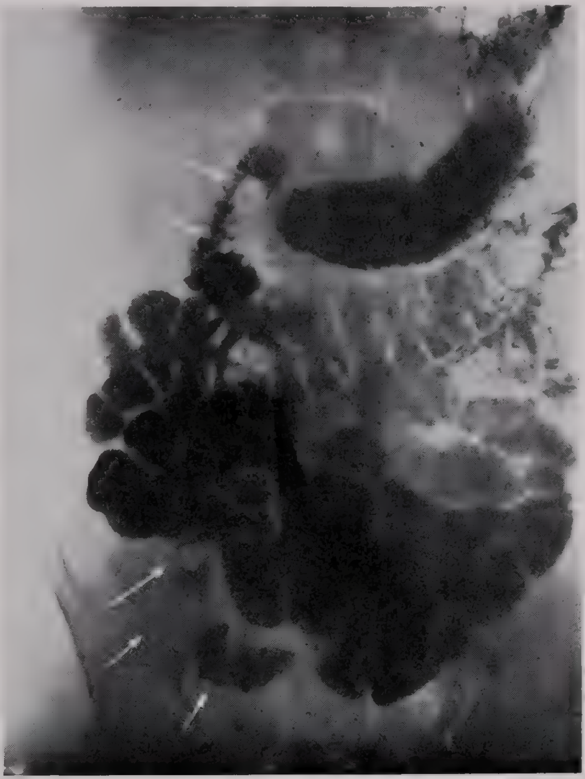


Fig. 6B—Another roentgenogram of same case. There are minor changes in the second and third portions of the duodenum seen in B (arrows) only.

The Golden Age

In the second half of the nineteenth century, the world of medicine at last abandoned the systems and dogmas that for centuries had done violence to the sick body. . . . At the bedside, the physician put aside his gold-headed can and approached the patient as a wise friend talking in simple language and offering rational therapies. His blend of science and practical experience inspired confidence, and his concern for the patient's comfort of body and mind won the patient's affection. Thus began the golden age of the general practitioner.

Charles Darwin enjoyed the care of such a family physician in Sir Andrew Clark, who tended him in the later years of his lifelong invalidism. Sir Andrew's friendly cheerfulness buoyed the despondent naturalist through his periodic bouts with headache, indigestion, vomiting, palpitations, dizziness, insomnia, and extreme fatigue.*

Editor's Note: Anyone who would go sailing on the Albatross for a couple of years must have had a restless spirit. It sounds to me like he was extremely functional and somewhat of a perfectionist. No doubt with this type of a disposition and temperament he found many of the everyday activities distressing to his sensitive soul. Well, everybody can't be a stoic!

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* The Patient's Progress, Edited by Marti-Ibanez, 1962.

Even a waiter sometimes comes to him who waits.—Herbert Prochnow

Morquio's Syndrome

Morquio's syndrome is an hereditary dystrophy of cartilage and bone that results in dwarfism and generalized skeletal deformity. Morquio and Brailsford, independently, in 1929 first described the essential features. The syndrome is transmitted as a recessive character; familial influences are common. There is a slight predilection for the male. The incidence is relatively rare.

Early manifestations of the developing dwarfism become apparent between the ages of four and 10 years. The spine is the most severely affected part of the skeletal system with curvature, kyphosis, shortening, and almost constant angulation at the dorsolumbar region. Chest deformity with increased anteroposterior diameter, forward thrust of the sternum, raised clavicles, and short neck become apparent as age increases. Other features include genu valgum and large feet with varus deformities. Lax ligaments, decreased muscle tone, joint crepitation and deformity, and delayed ossification of the epiphyses are frequently present. The combined abnormalities usually result in a duck-waddling gait. Roentgenograms of the skull are normal. Intelligence is usually unimpaired.

The cause of these developmental anomalies is not known. Differential diagnosis should exclude Hurler's syndrome, which is characterized by an enlarged shoe-shaped skull, hepatosplenomegaly, mental retardation, and corneal clouding. The wedge-shaped deformities of the vertebral bodies in Leri's syndrome may resemble those of Morquio's syndrome. Bone deformities in Morquio's syndrome are progressive, and there is increasing disability until walking becomes impossible.

Durham, Robert H.—Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York

The Slowly Moving Finger

In general, among all groups of organisms sharing a common plan of structure, the large ones live longer than the small. Among plants, the giant sequoia tree lives longer than the daisy. Among animals, the giant sturgeon lives longer than the herring, the giant salamander lives longer than the frog, the giant alligator lives longer than the lizard, the vulture lives longer than the sparrow, and the elephant lives longer than the shrew.

Indeed, in mammals particularly, there seems to be a strong correlation between longevity and size. There are exceptions, to be sure—some startling ones. For instance, whales are extraordinarily short-lived for their size. Most cetaceans are doing very well indeed if they reach 30. This may be because life in the water, with continuous loss of heat and the never-ending necessity of swimming, shortens life.

But much more astonishing is the fact that man has a longer life than any other mammal—much longer than the elephant or even than the closely allied gorilla. When a human centenarian dies, of all the animals in the world alive on the day that he was born, the only ones that remain alive on the day of his death (as far as we know) are a few sluggish turtles, an occasional ancient vulture or sturgeon, and a number of other human centenarians. Not one non-human mammal that came into this world with him has remained. All, without exception (as far as we know), are dead.*

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*Isaac Asimov: Of Time and Space and Other Things, 1965.

|| Myelography*

Past
and
Present
(1935-1968)

Harold O. Peterson, M.D.†
Minneapolis, Minnesota

As a measure of the esteem in which he was held by his fellow radiologists and in recognition of the many contributions he made to the developing field of radiology, three series of lectures have been established in memory of Russell Daniel Carman, M.D. The Minnesota Radiological Society instituted its Carman lectureship early in 1934. Later that same year, the Radiological Society of North America also initiated a Carman lecture which continued until recent years. In addition, the St. Louis Radiological Society sponsors a Carman lecture.

The roster of the 33 previous Carman lecturers to this society read like a "Who's Who" of radiology. I feel very humble indeed to be added to this great array of former lecturers, four of whom (A. B. Moore, M.D.—1934, B. R. Kirklin, M.D.—1946, C. A. Good, M.D. —1961, and L. G. Rigler, M.D.—1964) were members or former members of the society when they gave this lecture. As Dr. Good has remarked, "It is a double honor indeed to be invited to lecture to one's fellow members."

Dr. Carman was born in Iroquois, Ontario, on March 18, 1875. As a young child, he came with his mother to St. Paul where he received his grade and high school education. His premedical training was taken at the University of Minnesota, and in 1901 he received his M.D. from the Marion Sims-Beaumont Medical College of St. Louis (later merged with the St. Louis University School of Medicine). His career was from the beginning oriented toward medical aspects of the roentgen ray. There were no departments of radiology in those days, and individuals in various fields of medicine worked with this new diagnostic tool. Thus it was that Carman took post-graduate training under Dr. F. H. Baetger, Professor of Orthopedic Surgery at Johns Hopkins University and a man especially interested in the

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*Carman Lecture 1968.
Presented at the Fall Meeting of the Minnesota Radiological Society, 1968.

†Professor and Retiring Head, Department of Radiology, University of Minnesota Medical School.

applications of x-ray to medicine. He returned to St. Louis in 1903 and for the next ten years practiced radiology while teaching first at St. Louis University and later at Washington University.

In 1913, Dr. Carman was invited to become the first full time director of radiology at the Mayo Clinic. For the next 13 years, until his death on June 18, 1926, he learned, mastered and taught the art and science of radiology while developing one of the largest and most outstanding departments in the world. During this period he was also at different times President of the American College of Radiology and the Radiological Society of North America and was President-Elect of the American Roentgen Ray Society when he died. I do not believe any other radiologist has held all three positions. Within three months following his death, the American Roentgen Ray Society presented a plaque in his honor which stands today in the lobby of the Mayo Clinic.

Dr. Byrl Kirklin, a student, close associate, and successor to Carman at the Mayo Clinic, gave the first Carman lecture to the Radiological Society of North America in 1934.[1] His remarks at that time, which I would like to quote, give those of us who did not know Carman some insight into what made this man such an outstanding radiologist:

> "When Carman came to Rochester in 1913, he knew relatively little about gastrointestinal radiology. When he walked out of the screen room for the last time, . . . he was undoubtedly one of the ablest radiologic diagnosticians of gastric and duodenal disease in the world. How did he acquire this knowledge and skill? Not by sparkling brillance of mind or effortless inspiration, but by hard work, well applied.
>
> Carman's mental processes were simple, direct, almost invariably accurate, and above all thorough. . . . All that Carman knew, which was much, he learned at first hand and knew beyond all shadow of doubt. He knew the morbid anatomy of gastroduodenal disease in relation to its radiologic manifestations as few other men have ever known it. His mental picture of gastric cancer, for example, was not derived merely from drawings, or from photographs or lantern slides, but from its varied radiologic images, its appearance when the abdomen was opened, its gross aspects after removal, and its histologic structure as revealed by the microscope, all of which he synthesized into a coherent and practical conception of the disease. Thus Carman not only taught by trustworthy precept, but set an example which may well be followed by all radiologic diagnosticians."

John Camp, who presented the Radiological Society of North America Carman lecture in 1949, stated:[2] "Carman was great because of his uncanny powers of observation which he applied to his work in an effort to know the truth and impart it to others. Morning after morning, year in and year out, he spent in the operating room and in the pathology laboratory correlating the findings of the fluoroscopic room and the roentgenogram. He was not satisfied to be right or wrong, he must know why."

Myelography

Although no previous Minnesota Radiological Society Carman lecturer has discussed the subject of myelography, Camp delivered the Radiological Society of North America Carman lecture in 1949 under the title "Contrast Myelography Past and Present".[2] He covered the subject extremely well. Indeed, there have been no major advances in myelography since 1950. I have chosen the same title today and hope to add some minor points from my own experience in the areas of myelographic technique and anatomy and in the myelographic diagnosis of disc disease.

Air Myelography

The history of myelography dates back to 1919, at which time Dandy predicted the usefulness of air myelography in his classical paper on encephalography.[3] The first deliberate air myelograms, however, were performed by a Swedish internist, Jacobeus, later that same year. He reported his first three cases in 1921.[4] In 1925, Dandy published his first 36 cases of air myelography as a method for detection and localization of spinal cord tumors.[5]

Lipiodol

In 1921, two French internists with some interest in neurology, Sicard and Forestier, were injecting lipiodol into the lumbosacral extradural space for the treatment of inflammatory disease. By accident, they introduced a small amount of this iodinated oil into the subarachnoid space of one patient and immediately recognized the usefulness of this contrast agent in the diagnostic evaluation of the spinal canal. Their discovery, first published in 1922,[6] was widely accepted, and lipiodol myelography became the method of choice for radiographic diagnosis of spinal cord tumors in the 1920's and 1930's. Small amounts of this contrast medium were employed in these early years, usually one quarter to one half c.c. introduced via cisternal puncture with films made in the upright position to locate the site of block. However, shortly thereafter, reports appeared noting the occurrence of adhesions and arachnoiditis due to residual lipiodol. It is probably for this reason that Swedish radiologists have had an aversion to the widespread use of oily contrast media for myelography up to this day. However, American radiologists felt that the advantages outweighed the disadvantages and advocated the use of even larger amounts (up to 3 cc.) in the evaluation of possible spinal cord tumors.

It was not until the historic paper of Mixter and Barr on the clinical significance of the ruptured intervertebral disc in 1934[7] that myelography became a very common procedure. Hampton and Robinson published the first radiological paper on the use of lipiodol for the diagnosis of herniated disc in 1936.[8] They advocated slightly larger amounts of contrast medium (up to 5 cc.), and this initiated further concern regarding the late effects of lipiodol in the subarachnoid space.

In 1939, Adson, a neurosurgeon at the Mayo Clinic, described a method of removing the contrast medium from the subarachnoid space by doing a small sacral laminectomy, incising the dura and then placing the patient erect, thus permitting evacuation of the contrast medium by gravity.[9] Shortly thereafter Kubik and Hampton in 1941[10] described the removal of lipiodol by aspiration through the original puncture needle, and this method is accepted up to the present date. Although lipiodol was not ideal for myelography (not only because of its tendency to promote the formation of arachnoiditis and adhesions, but also because of its rather high viscosity), it was then and is still today a very good contrast medium because of its radiopacity.

The search for a better contrast medium led Nosik to recommend Thorotrast in 1938.[11] However, it was soon apparent that although this colloidal thorium preparation yielded technically satisfactory myelograms, it was quite difficult to remove from the subarachnoid space. Thorotrast, of course, is radioactive with an extremely long half-life, and we are today seeing the unfortunate results of residual Thorotrast in the spinal canal, including nerve root and spinal cord damage as well as the possibility of radiation-induced neoplasms.

In 1940, Camp designed the first 90/90 tilt table for myelography. Up to that time, tilt tables were limited in their motion in one direction to 15/30 degrees. This table was produced by Keleket, and we were fortunate in obtaining one of these tables in 1942 at the Miller Hospital. This greatly facilitated myelography in the thoracic and cervical regions.

Pantopaque

In 1942, the studies of Strain, Plati, and Warren on pantopaque were published.[12] This ethyl ester of iodophenylundecylic acid was not as viscous as lipiodol and thus was easier to aspirate. For the past 25 years, pantopaque has been the contrast medium of choice in this country for myelography. The Swedes continue to work with water-soluble contrast media which do not have to be aspirated.[13] These, however, require spinal anesthesia and thus are limited to examination of the lumbar region. Water-soluble contrast myelography has never become popular in this country. The ideal myelographic contrast medium, of course, would be administered orally, parenterally, or intrathecally and would be completely absorbed from the subarachnoid space after a short period of time with no meningeal reaction.

Technique of Myelography

I believe that myelography should be done in a manner that is painless. Since the contrast medium is not water soluble and must be aspirated at the conclusion of the procedure, introduction of the spinal needle should be done under fluoroscopic control so as to obtain a midline placement. If the needle is in the midline, aspiration of the pantopaque bolus is markedly facilitated. An off-center puncture increases the probability that nerve roots may be impaled during the puncture or aspirated against the needle during aspiration, resulting in radicular pain. It is also best to avoid introducing the needle directly over a disc space; under fluoroscopic control, this is a relatively easy task. In general, it is wise to proceed slowly and gently, advancing the needle in small increments. Once free flow of cerebrospinal fluid is obtained, the needle is advanced another millimeter so that the entire length of the bevelled tip lies within the subarachnoid space. Occasionally, however, the dura or arachnoid may be only partly penetrated by the needle. Further advancement of the needle will then depress the dura or arachnoid, producing defects in the pantopaque column and resulting in a difficult aspiration.

The subdural injection of pantopaque is an occasional complication and should be recognized (Figure 1). When it is recognized, one should never make any type of diagnosis at all other than that one has a subdural injection. Recognition of a subdural injection depends on a fairly sharp almost knifeblade-shaped collection of the contrast medium with indistinct margins.

Most subdural injections are posterior. With the patient prone, the lateral view reveals the contrast medium on the dorsal aspect of the sac. Removal of the contrast medium is difficult, but gentle patient perseverance will usually allow the aspiration of a high proportion of the subdurally injected bolus.

Except in rare instances, no special preparation is required for myelography. However, an occasional patient has so much pain from a disc herniation that he cannot lie on his abdomen for a myelogram. In these cases, it is acceptable to do a puncture in a more comfortable position, aspirate a few cc. of cerebrospinal fluid and dissolve 50 to 75 milligrams of procaine crystals in this fluid. The resulting solution is then reinjected into the subarachnoid space and usually results in very prompt relief of the radicular pain. One can then place the patient prone on the fluoroscopic table and perform a satisfactory myelogram.

Volume of Pantopaque

With regard to how much contrast medium should be used, I have felt more and more in recent years that the quantity should be sufficient to completely outline the sac in the area of suspected clinical abnormality. In the lumbar region, 6 cc. of pantopaque may completely fill a narrow subarachnoid space up to the level of L1. However, in a patient with a very large sac, 50 cc. may barely fill the sac up to the L4-5 disc space. The examination should be tailored to the size of the sac and the location and nature of the suspected abnormality. I do not feel that one should be limited to the use of 6 cc. or any other particular volume. Inadequate volumes of contrast medium in the thoracic region will only outline the anterior aspect of the sac, and le-

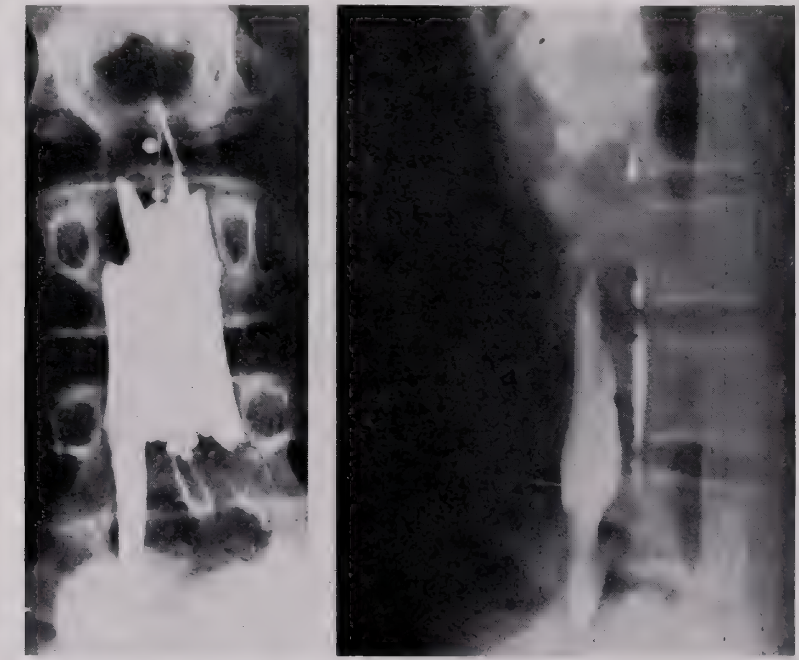

Fig. 1—Subdural injection of pantopaque. (A—left) Anteroposterior view demonstrates sharp almost knifeblade-shaped margins of the collection of contrast medium. There are a few globules of pantopaque which are subarachnoid in location. (B—right) Lateral projection with patient prone shows the subdural contrast medium located posteriorly within the spinal canal. The few droplets in the subarachnoid space lie anteriorly.

sions involving the mid or posterior aspects of the spinal cord will be missed. In the lumbar region, a small amount of pantopaque may pool in the shallow concavities on the posterior aspects of the lumbar vertebral bodies, giving the false appearance of multiple protruding intervertebral discs. Introduction of larger amounts of pantopaque will demonstrate the true anatomy and avoid a false diagnosis of herniated disc. In order to rule out the possibility of an intramedullary arteriovenous malformation, we have used volumes as large as 105 cc. to demonstrate the entire circumference of the spinal cord and thecal sac in the lumbar, thoracic, and cervical regions.

Larger amounts of pantopaque are no more difficult to remove than smaller boli. If there is any difficulty, it usually occurs in aspiration of the last half cc. and the amount of contrast medium employed does not affect this difficulty.

One objection that has been raised to the use of larger amounts of pantopaque is that the rather dense contrast medium (iodine concentration 30%) may obscure underlying lesions. A recent evaluation in our department of a half-strength pantopaque (iodine concentration 15%) failed to substantiate this objection.

Larger amounts of pantopaque are of value in the examination of patients with severe scoliosis, in the demonstration of lesions on the posterior aspect of the thecal sac, and in almost any process other than a complete block which is located in the thoracic or upper lumbar area. Cervical myelography is also greatly facilitated by the use of at least 12 cc. and usually more pantopaque.

The Lumbar Herniated Disc

The classical picture of a herniated intervertebral disc in the lumbar region as described originally by Hampton and Robinson in 1936[8] is still valid. A sharply defined unilateral anvil-like filling defect along the lateral margin of the contrast column at the disc space level is the most valid myelographic finding suggesting herniated intervertebral disc and almost without exception correlates well with surgical findings (Figure 2). This type of deformity is almost always located at the L4-5 level. Nearly 90% of lumbar disc herniations occur at either the L4-5 or L5-S1 levels.[14] The great majority of the remainder occur at L3-4. A lateral projection with the patient in the prone position is often helpful in demonstrating a double shadow on the ventral aspect of the radiopaque column due to a relatively normal posterior disc margin on one side and a more dorsally displaced margin on the side of the herniation. Since the nucleus often herniates through the annulus in a posterolateral direction, anterior

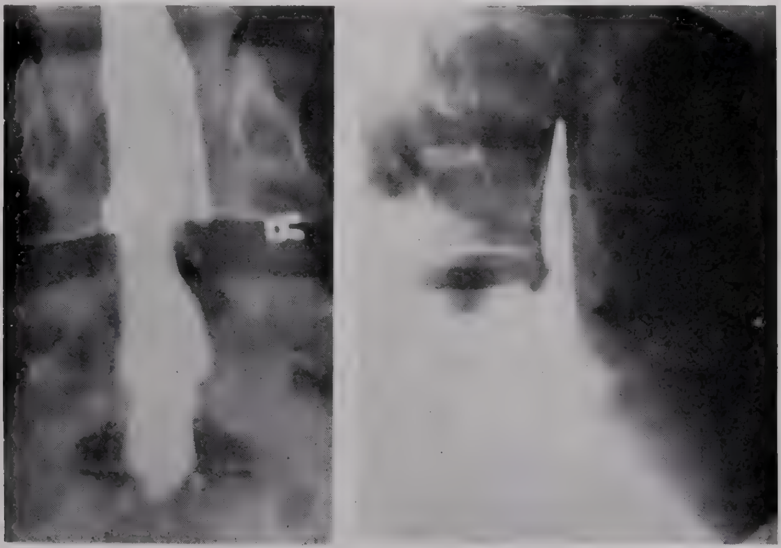

Fig. 2—Herniated intervertebral disc, L4-5 on the right side. (A—left) Anteroposterior view shows sharply defined anvil-like filling defect along lateral margin of pantopaque column at level of L4-5 disc space. (B—right) Lateral projection with patient prone demonstrates a double shadow on the ventral aspect of the radiopaque column due to more dorsally displaced margin on the side of the herniated disc.

oblique views are often of considerable aid in diagnosis.

The pathologic studies of Horwitz in the 1940's established the frequency of bulging and even herniated intervertebral discs in asymptomatic patients.[15] Recent post-mortem discographic and anatomic studies in our department demonstrate a 35% incidence of herniated intervertebral discs at the L3-4 and L4-5 levels in patients above the age of 40. Thus, the mere myelographic demonstration of an extradural anterolateral deformity consistent with a herniated disc is not always the cause of the patient's symptoms. The myelographic findings must always be correlated with the patient's clinical signs and symptoms.

The diagnosis of the occasional herniated disc in the upper lumbar and lower thoracic region requires the use of large amounts of contrast medium so as to build up a "full column" to the level of suspected abnormality. The use of small amounts (6 to 12 cc.) in this region unduly accentuates minor elevations at disc levels which are so common in the older age groups and are usually not significant. The contrast medium tends to pool along the anterior aspect of the sac near the midline in the normally concave curvature of the dorsal aspect of the vertebral body which is accentuated in some individuals. The lateral margins of the intervertebral disc being at a higher level causes a thin pantopaque column to pool toward the midline. On the frontal projection, this results in an hourglass type of deformity which is usually not significant and can be greatly minimized with larger amounts of pantopaque (Figure 3).

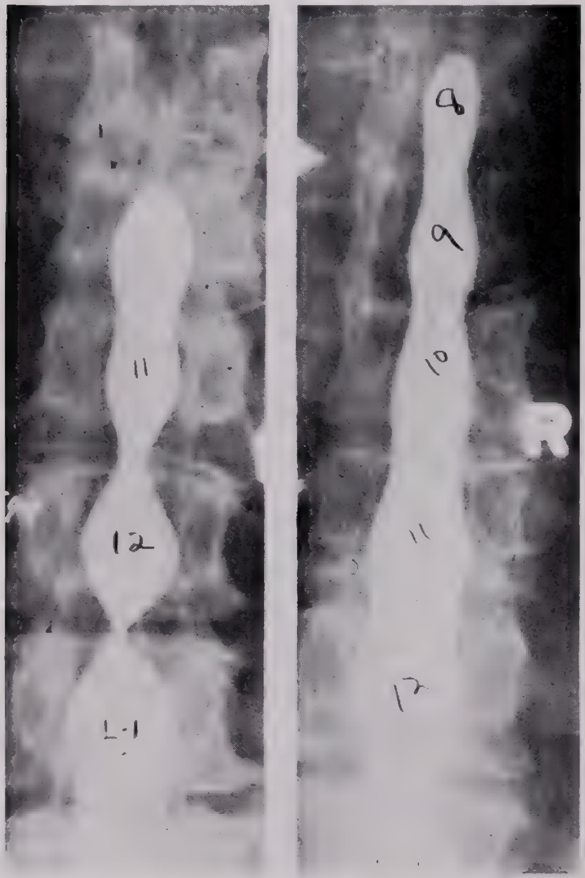

Fig. 3—Hourglass configuration due to small amount of pantopaque. (A—left) 12 cc. pantopaque. Bilateral identations on lateral margins of contrast column at T11-12 and T12-L1. (B—right) 24 cc. pantopaque. The bilateral indentations have disappeared (see text).

The size of the bony spinal canal may cause problems in technique as well as in diagnosis. There is a significantly large number of people who are born with short pedicles and a resultant narrow anteroposterior diameter of their spinal canals. Minor degrees of disc bulging with or without symptoms may produce varying degrees of dural sac compression in these patients

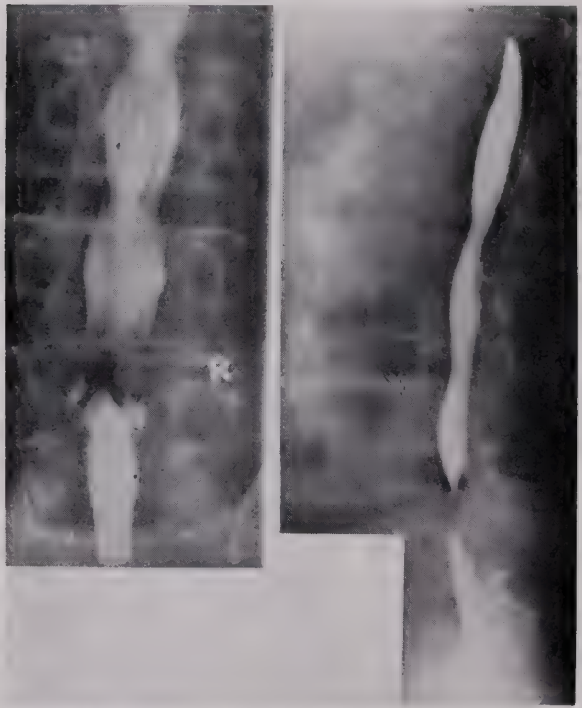

Fig. 4—Narrow anteroposterior diameter of spinal canal. (A—left) Anteroposterior projection. Partial extradural block at level of L4-5 disc space. Note prominence of nerve roots due to thin column of pantopaque. (B—right) Lateral view demonstrates significant narrowing of spinal canal in sagittal plane in lumbar region. Partial block at L4-5 due to disc bulging on anterior aspect and ligamentous thickening posteriorly.

with striking radiographic findings. Myelography may reveal compression of the thecal sac not only from the anterior aspect, but also bilaterally and in some cases even from the posterior surface of the sac (Figure 4). Exploration may reveal marked thickening of the soft tissues in the epidural space, the ligamenta flava posterolaterally, and the soft tissues surrounding the apophyseal joints. It is possible that the relatively minor degrees of trauma to which we are all exposed in everyday life are more significant in such patients because of the narrow spinal canal. Myelography is often very difficult to perform in such patients because of the narrow sac, but a good myelogram may be indispensable to planning an adequate surgical procedure for relief of the chronic and often atypical symptoms with which these patients present.

Recurrence of low back pain, sciatica, and neurological deficits following laminectomy for herniated disc is not rare. However, myelography in such patients is fraught with the possibility of error. Many deformities may be seen postoperatively which may be the result of previous surgical exploration (Figure 5). While one cannot rule out the posibility of a recurrent disc herniation underlying the deformed sac, it is wise not to make this diagnosis unless the deformity is quite classical.

Conclusions

Myelography is an established radiologic procedure for the evaluation and localization of diseases within and affecting the spinal canal. The amount of contrast medium employed in the examination should vary with the size of the thecal sac, the level to be examined, and the nature of expected pathology; but in general larger volumes (more than 12 cc.) will give a more accurate and reliable examination than the small amounts used in an earlier era. Careful meticulous technique with the examination being performed under fluoroscopic control from beginning to end should produce little or no patient discomfort. The diagnosis of herniated intervertebral disc in the lumbar region can usually be accurately made with myelography. However, because of the frequency of asymptomatic disc degeneration particularly in patients beyond age 40, the treatment of the individual case must be based on keen clinical judgment and experience together with a judicious analysis of a technically perfect myelogram.

On the occasion of Dr. Carman's untimely death, his life-long friend and associate Dr. Albert Miller wrote: "The world of the x-ray lost a master workman. For a time it will grieve that he is dead. For a longer time it will rejoice that he lived."

I feel greatly honored that I should be permitted this opportunity of participating in this tradition of the Minnesota Radiological Society which brings to each annual meeting the spirit of one who loved his profession and who exemplified the highest ideals of medicine.

Acknowledgment

The author wishes to acknowledge the aid of Dr. Stephen A. Kieffer in the editing of this manuscript for publication.

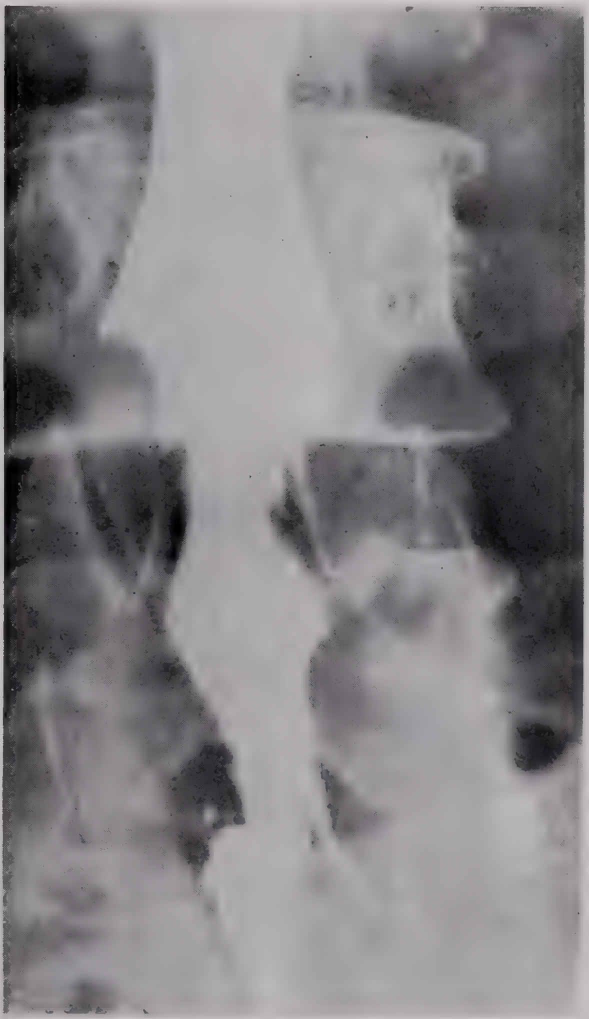

Fig. 5—Unusual angular indentation on lateral margin of pantopaque column at level of fifth lumbar vertebra in patient with history of previous laminectomy at this level. Deformity likely related to previous surgical exploration.

References may be secured from the author or the reprints.

Nobel Prize Winners in Medicine and Physiology

1907

Charles Louis Alphonse Laveran

In recognition of his work regarding the role played by protozoa in causing disease

"On arriving at Bona in 1878 I had the opportunity of making autopsies on subjects who had died from pernicious attacks, and I was struck with the fact that melanaemia was a lesion peculiar to and very characteristic of paludism;* my attention was naturally directed to this lesion, which I had never met in any other disease.

"When one examines a drop of blood taken from the dead body of a palustral subject in the ordinary conditions of autopsy—that is to say, twenty-four hours after death—one sees in the midst of the blood numerous pigmented bodies. Many of these elements are melaniferous leucocytes, the nuclei of which can be coloured and stained with carmine; but besides these leukocytes, hyaline pigmented irregular bodies are seen, which can only be coloured slightly, or not at all, by carmine, and which do not contain any nuclei.

"In 1880, as I was trying to account for the mode of formation of the pigment in the palustral blood, I was led to see that besides melaniferous leucocytes, spherical hyaline corpuscles without nucleus could be seen, and also very characteristic crescent-shaped bodies.

"I had proceeded thus far with my researches, and was still hesitating whether these elements were parasites, when on November 6th, 1880, on examining the pigmented spherical bodies mentioned above, I observed, on the edge of several of these elements, movable filaments of flagella, whose extremely rapid and varied movements left no doubt as to their nature.

"I published in 1881 the observation of the patient in whose blood I saw the flagella for the first time."*

Laveran's discovery of the malarial parasite did not receive immediate recognition from all authorities, but his findings were soon confirmed and extended by others, and his own pathological, clinical, geographical, and therapeutic studies all tended to establish the role of the organisms he had discovered, which later came to be known as plasmodia. Their presence in the blood of malaria patients, their disappearance after treatment with quinine, their absence in healthy persons, and their association with the characteristic malaria pigment made it highly probable that they were indeed the long-sought causative organisms of malaria.†

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*Alphonse Laveran: Paludism, translated by J. W. Martin in 1893.
†Theodore Sourkes: Nobel Prize Winners in Medicine and Physiology, 1966.

Science

I have seen the science I worshipped and the aircraft I loved destroying the civilization I expected them to serve, while the life-saving miracles of medicine are being perverted toward the murderous ends of biological warfare.

—*Charles Lindbergh*

Worry

Worry, according to a contemporary biochemist, "can be chemically defined as the psychic reaction of somatic saturation with paralytic acid and monosodic phosphate."—Dr. M. N. Eisendrath.

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patients from exhaustion

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Precautions: Lomotil is a Federally exempt narcotic with theoretically possible addictive potential at high dosage; this is not ordinarily a clinical problem. Use Lomotil with considerable caution in patients receiving addicting drugs. Recommended dosages should not be exceeded, and medication should be kept out of reach of children. Should accidental overdosage occur, signs may include severe respiratory depression, flushing, lethargy or coma, hypotonic reflexes, nystagmus, pinpoint pupils, tachycardia; continuous observation is necessary. The subtherapeutic amount of atropine sulfate is added to discourage deliberate overdosage.

Adverse Reactions: Side effects reported with Lomotil therapy include nausea, sedation, dizziness, vomiting, pruritus, restlessness, abdominal discomfort, headache, angioneurotic edema, giant urticaria, lethargy, anorexia, numbness of the extremities, atropine effects, swelling of the gums, euphoria, depression and malaise. Respiratory depression and coma may occur with overdosage.

Dosage: The recommended initial daily dosages, given in divided doses until diarrhea is controlled, are as follows:

Children:	*Total Daily Dosage*
3-6 mo.	½ tsp.* t.i.d. (3 mg.)
6-12 mo.	½ tsp. q.i.d. (4 mg.)
1-2 yr.	½ tsp. 5 times daily (5 mg.)
2-5 yr.	1 tsp. t.i.d. (6 mg.)
5-8 yr.	1 tsp. q.i.d. (8 mg.)
8-12 yr.	1 tsp. 5 times daily (10 mg.)
Adults:	2 tsp. 5 times daily (20 mg.) or 2 tablets q.i.d.

*Based on 4 cc. per teaspoonful.

Maintenance dosage may be as low as one-fourth the initial daily dosage.

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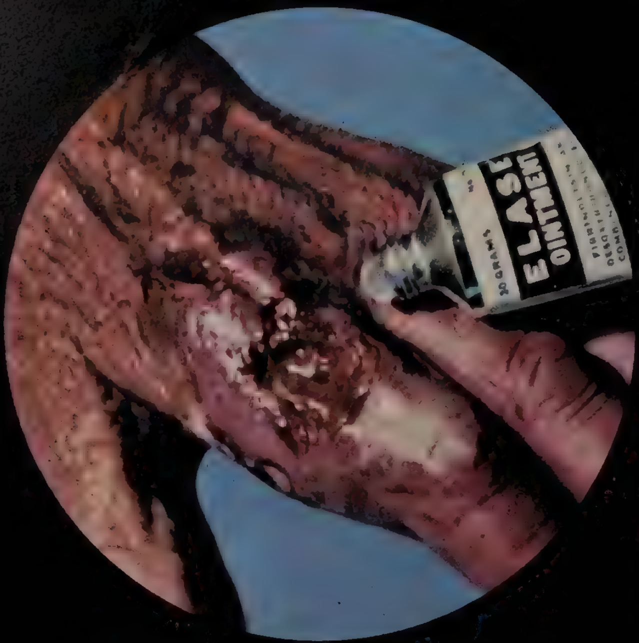
this ulcer did not heal...until its surface was cleared of dead tissue and debris



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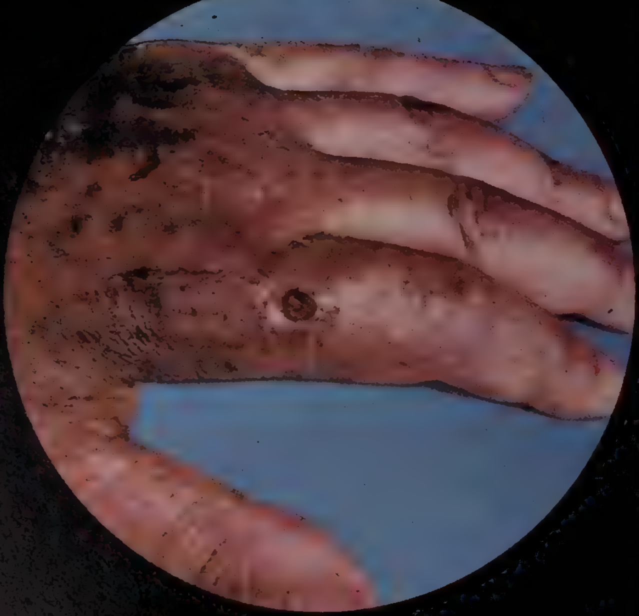

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48168

Pulmonary Function

A Study in the Baboon Using Xenon-133 and a Scintillation Camera*

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THE XENON-133 TECHNIC of measuring regional pulmonary function represents a significant advance in the study of respiratory physiology. Xe-133 emits a low energy gamma ray of 81 kev. that is suitable for detection by radiation (scintillation) detectors. It is inhaled in gas form for study of ventilation, and injected intravenously in saline solution for study of pulmonary blood flow. Because of its low solubility, the injected xenon evolves into gas as soon as it reaches the lung. Xe-133's short biological half-life permits administration of adequate doses and repeated examinations without undue radiation hazard to the patient. Unlike bronchospirometry, the xenon technique is performed with the patient in sitting position without intubation. The results obtained by the two methods have been very comparable.[6]

In the original methods described by Ball and associates[1] and by West and Dollery[8] multiple scintillation detectors were placed over the chest wall, enabling strip chart recording of the radioactivity of Xe-133 in different zones of the lungs. The recent advent of Anger's scintillation camera has made it possible to cover the entire thorax with a single large scintillation detector and to document the radioactivity of various zones of each lung both graphically on strip charts and pictorially as scintiphotos on Polaroid films.[2,3,5] With proper interface equipment one can advance to computer processing of data. At the University of Minnesota Nuclear Medicine Clinic,[4] data from the scintillation camera are passed directly to a 1600 word memory system which is in the form of a 40 × 40 matrix. From this storage it is transferred at three-second intervals to magnetic tape which is then analyzed using a CDC 3300 computer.

With the increasing interest in organ transplantation it is expected that the xenon technic

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*Supported by the James Picker Foundation on recommendation of the Committee on Radiology, National Academy of Sciences—National Research Council.

†From the Departments of Radiology, Hennepin County General Hospital (Minneapolis Medical Research Foundation), and University of Minnesota Medical School, Minneapolis, Minnesota.

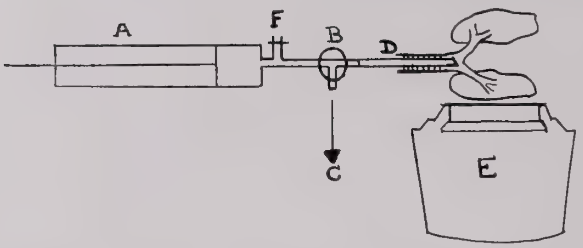

Fig. 1—A. Pump. B. 3-way tap. C. Exhaust. D. Endotracheal tube. E. Detector head. F. Fresh air inlet.

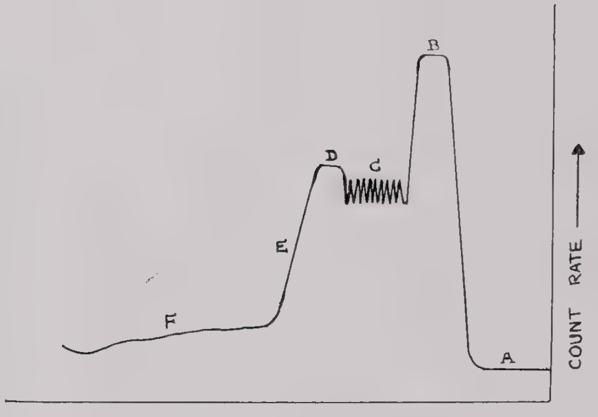

Fig. 2—Strip chart tracing of radioactivity of one lung during either perfusion or ventilation study. A. Initial background activity. B. Initial plateau following injection or inhalation of xenon-133. C. Rebreathing. D. Plateau after rebreathing. E. Washout period. F. Final background activity.

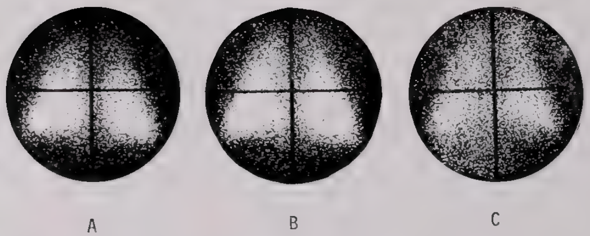

Fig. 3—Serial scintiphotograms made during either perfusion or ventilation study. A. During initial plateau after Xe-133 injection or inhalation. B. During plateau after rebreathing. C. During washout period (note diffuse activity in chest wall).

will be of value in assessing the function of lung transplants. The present work was initiated to establish a baseline for regional pulmonary function in 12 normal Kenya baboons which will be used in the lung transplantation program at Minneapolis Medical Research Foundation. The anesthetised animal was placed supine in a V-shaped lucite tray which in turn was placed on a wooden rack. The tray and rack were placed directly over the detector head of the scintillation camera.

Method

An endotracheal tube was introduced and connected to a one-liter hand pump via a three-way tap as described by Pain et al.[7] With the cuff inflated and the three-way tap turned off exhaust, the endotracheal tube, the lungs, and the pump formed a closed system (Figure 1). The animal could be made to inhale air delivered from the pump. Breath-holding was achieved by holding the piston down. Rebreathing was done by moving the piston back and forth. To wash the radioactive xenon out of the lungs the animal was made to inhale 500 ml. of fresh air from the pump and exhale passively through the exhaust. This was done 10 times.

Determination of Pulmonary Perfusion

Five to 10 mc. of Xe-133 in 5-10 ml. of saline were injected intravenously. At the end of injection, by means of the pump, the animal was made to inhale 500 ml. of air and breath-hold. As the xenon entered the lungs via the pulmonary artery, the dual chart recorders registered an abrupt rise of radioactivity. When the activity in each lung had reached a plateau (Figure 2-B), the animal was rebreathed 10 times at a tidal volume of 500 ml. (Figure 2-C) to achieve uniform intrapulmonary distribution of the evolved xenon gas. This was followed by a five to six-second period of breath-holding (Figure 2-D) and a subsequent washout procedure (Figure 2-E). A in Figure 2 was the initial background activity; and F, the final background activity. F was greater than A because of contributions from the xenon that had reached the chest wall.

The count rate at plateau B, corrected for initial background, is an index of the blood flow of the lung; while that at plateau D, corrected for final background, the alveolar volume. Dividing the former by the latter one obtains an expression of the *perfusion per unit alveolar volume of the lung.*[7]

Throughout the entire examination the analog data were converted to digital form and taped. Serial scintiphotos were also made on Polaroid films at points corresponding to B, D, and E in Figure 2 (Figure 3).

Determination of Ventilation

Five to 10 mc. of Xe-133 gas were deposited in the lumen of the endotracheal tube. This, together with 500 ml. of air from the pump, was inhaled by the animal. Breath was held until the dual chart recorders showed plateauing of the radioactivity in each lung (Figure 2-B). Rebreathing, a second breath-holding and the final washout process were carried out as in the study for perfusion (Figures 2-C, D, E), as were data conversion, data storage, and scintiphotography (Figure 3).

The count rate at B, corrected for initial background, is an index of ventilation of the lung; and that at D, corrected for final background, the alveolar volume. The ratio of the two represents *ventilation per unit alveolar volume of the lung.*[7]

Results

Relative Pulmonary Perfusion

Five of the 12 baboons had pulmonary blood flow determinations on two occasions, while the other seven were examined only once. There were thus a total of 17 determinations and 34 readings.

The computer was programmed to supply, among other data, left lung/right lung ratios in the following categories: perfusion, alveolar volume, perfusion per unit alveolar volume, and washout half-time (i.e., the number of seconds needed to reduce the corrected count rate at plateau D in Figure 3 by half). A left/right ratio of 1.0 for perfusion would mean a relative blood flow distribution of 50% on each side; a ratio of 0.90, a distribution of 47.3% on the left and 52.7% on the right, etc.

Tables 1 and 2 show the good agreement between duplicate readings in 17 determinations and between readings in animals that had two separate determinations. In either case, the index of *perfusion per unit alveolar volume* was

TABLE 1

Reproducibility of Duplicate Readings in 17 Determinations of Relative Pulmonary Perfusion

Left Lung/Right Lung Ratio	Mean	Standard Deviation
Perfusion:		
1st readings	0.97	0.35
2nd readings	0.94	0.31
All readings	0.94	0.31
Alveolar volume:		
1st readings	0.95	0.23
2nd readings	0.90	0.24
All readings	0.92	0.23
Perfusion/unit alveolar vol.:		
1st readings	1.00	0.16
2nd readings	1.00	0.12
All readings	1.00	0.14
Washout half-time:		
1st readings	1.22	0.50
2nd readings	1.03	0.27
All readings	1.13	0.41

TABLE 2

Reproducibility of Readings on 2 Separate Determinations of Relative Pulmonary Perfusion in 5 Animals

Left Lung/Right Lung Ratio	Mean	Standard Deviation
Perfusion:		
1st determination (all readings)	0.81	0.16
2nd determination (all readings)	0.98	0.31
Alveolar volume:		
1st determination (all readings)	0.84	0.26
2nd determination (all readings)	0.98	0.22
Perfusion/unit alveolar volume:		
1st determination (all readings)	0.98	0.11
2nd determination (all readings)	0.98	0.11
Washout half-time:		
1st determination (all readings)	1.26	0.50
2nd determination (all readings)	1.11	0.45

the most reproducible; the washout half-time, the least reproducible.

The computer was also programmed to give the left/right ratios of perfusion, alveolar volume, perfusion per unit alveolar volume and washout half-time in the upper, middle, and lower thirds of the lung. Tables 3 and 4 compare the reproducibility of readings applicable to the lower thirds. Here the index of perfusion per unit alveolar volume was the most reproducible on duplicate readings in all determination; but less so on two separate determinations in the same animal.

Relative Pulmonary Ventilation

Half of the 12 baboons had a single determination; the other half, two separate determinations. Duplicate readings were obtained at each examination. Reproducibility of the readings was relatively poor except perhaps for alveolar volume (Tables 5 and 6). The data for regional ventilation of the upper, middle and lower lungs showed even wider variations.

Discussion

The present method measures the regional function of each lung, or, with the aid of the data system and the programmed computer, any portion of the lung. Both perfusion and ventilation are evaluated. The readings for perfusion, particularly the *perfusion per unit alveolar volume,* are very reproducible.

TABLE 3

Reproducibility of Duplicate Readings in 17 Determinations of Relative Perfusion of Lower Thirds of Lungs

Left Lower Lung/Right Lower Lung Ratio	Mean	Standard Deviation
Perfusion:		
1st readings	0.93	0.31
2nd readings	0.89	0.29
All readings	0.91	0.30
Alveolar volume:		
1st readings	0.91	0.19
2nd readings	0.89	0.29
All readings	0.90	0.30
Perfusion/unit alveolar volume:		
1st readings	1.03	0.19
2nd readings	1.03	0.27
All readings	1.03	0.23
Washout half-time:		
1st readings	1.00	0.33
2nd readings	1.01	0.24
All readings	1.00	0.29

TABLE 4

Reproducibility of Readings on 2 Separate Determinations of Relative Perfusion of Lower Thirds of Lungs in 5 Animals

Left Lower Lung/Right Lower Lung Ratio:	Mean	Standard Deviation
Perfusion:		
1st determination (all readings)	0.80	0.20
2nd determination (all readings)	0.95	0.30
Alveolar volume:		
1st determination (all readings)	0.82	0.24
2nd determination (all readings)	0.90	0.16
Perfusion/unit alveolar volume:		
1st determination (all readings)	1.01	0.16
2nd determination (all readings)	1.06	0.29
Washout half-time:		
1st determination (all readings)	1.07	0.30
2nd determination (all readings)	1.09	0.34

The poor reproducibility of ventilation values was due to several factors. First, intubation of the short baboon trachea required special care, because either bronchus was easily blocked if the endotracheal tube was placed too low. It was also likely that the bevel of the tube sometimes caused preferential flow of the air and xenon towards the side it was facing. A third factor was the long anesthesia time. The baboons were first anesthetized at the Minneapolis Medical Research Foundation and then transported to the University of Minnesota Nuclear Medicine Clinic for the examination. The minimum total anesthesia time was two and a half hours. During this period secretions sufficient to occlude one or more bronchial branches may have accumulated. We believe that, with a properly placed tube and a dry tracheo-bronchial tree, the repeatability of ventilation readings will be acceptable.

Conclusion

The method as described here should be satisfactory for assessing regional pulmonary function in the experimental animal.

Acknowledgment

The authors gratefully acknowledge the assistance of George Kush in computer programming and Pearl Ahlstrom, R.N., in preparing the illustrations.

References may be secured from the author or the reprints.

TABLE 5

Reproducibility of Duplicate Readings in 17 Determinations of Relative Pulmonary Ventilation

Left Lung/Right Lung Ratio	Mean	Standard Deviation
Ventilation:		
1st readings	0.91	0.43
2nd readings	1.36	1.08
All readings	1.12	0.69
Alveolar volume:		
1st readings	1.10	0.45
2nd readings	1.06	0.25
All readings	1.08	0.33
Ventilation/unit alveolar volume:		
1st readings	0.86	0.35
2nd readings	1.30	1.06
All readings	1.07	0.79
Washout half-time:		
1st readings	1.04	0.33
2nd readings	0.88	0.22
All readings	0.96	0.27

TABLE 6

Reproducibility of Readings on 2 Separate Determinations of Relative Pulmonary Ventilation in 5 Animals

Left Lung/Right Lung Ratio	Mean	Standard Deviation
Ventilation:		
1st determination (all readings)	1.35	1.33
2nd determination (all readings)	1.13	0.37
Alveolar volume:		
1st determination (all readings)	0.97	0.20
2nd determination (all readings)	1.11	0.26
Ventilation/unit alveolar volume:		
1st determination (all readings)	1.41	1.31
2nd determination (all readings)	1.04	0.32
Washout half-time:		
1st determination (all readings)	1.02	0.41
2nd determination (all readings)	0.92	0.31

In Memoriam

Death, like birth, is a secret of Nature.—Marcus Aurelius

PAUL H. HEDENSTROM, M.D.

Dr. Paul H. Hedenstrom, 43, head of the Princeton Medical and Surgical Center, was killed October 10 in a light plane crash. Dr. Hedenstrom came to Princeton in 1967, when he joined the McManus Clinic. Prior to that time he had practiced at the St. Cloud Hospital, where he was a member of the Surgical Privileges Committee. He was also consulting surgeon for St. Gabriels Hospital in Little Falls.

Certified by the American Board of Surgery as a diplomate, he was also a member of the American Medical Association, the Minnesota State Medical Association, and the Stearns-Benton County Medical Society.

Dr. Hedenstrom is survived by his wife, a son and daughter.

KEITH D. LARSON, M.D.

Dr. Keith D. Larson, 54, former medical director of the Moose Lake State Hospital, died suddenly September 21, in Washington. He was a native of Clintonville, Wisconsin, and graduated from Lawrence College, Appleton, and Northwestern University Medical School in Chicago. He interned at the Presbyterian Hospital in Chicago and took his residency at the Cook County Hospital. Later he received his fellowship at the Mayo Clinic specializing in neurology, psychiatry and internal medicine.

Dr. Larson is survived by his wife and three daughters.

HOWARD M. FRYKMAN, M.D.

Dr. Howard M. Frykman, 52, Minneapolis proctologist, died October 2. Born in Souris, North Dakota, he attended the University of Minnesota Medical School.

Dr. Frykman was a member of the American Medical Association, the Minnesota State Medical Association and the Hennepin County Medical Society.

He is survived by his wife and children.

FREDERICK L. SMITH, M.D.

Dr. Frederick L. Smith, 90, emeritus head of the section of the postoperative treatment at the Mayo Clinic, died September 14, of a heart ailment. Born in Waseca, Minnesota, Dr. Smith attended the University of Minnesota Medical School.

His professional affiliations were numerous, including membership in the American Medical Association, the Alumni Association of the Mayo Foundation, the Association of the Military Surgeons of the United States. He was a charter member of the Minnesota Academy of Science and a former president of the Olmsted County Medical Society. Dr. Smith was an Associate and 50 Club Member of the Minnesota State Medical Association.

He is survived by his wife, one daughter and two sons, one of whom is Dr. Frederick A. Smith of Bath, New York.

EDWARD R. ADDY, M.D.

Dr. Edward R. Addy, 69, Gilbert physician, died July 9, after a lingering illness. Born in Northville, North Dakota, he attended the University of Minnesota Medical School and interned at St. Mary's Hospital in Duluth. He came to Gilbert in 1933, where he practiced medicine until the time of his illness.

He was a member of the American Academy of General Practice, the American Medical Association, the Minnesota State Medical Association and the Range Medical Society.

He is survived by his wife.

FRANK J. HIRSCHBOECK, M.D.

Dr. Frank J. Hirschboeck, 82, Duluth physician, died October 15. He had been associated with the Duluth Clinic for forty-four years. His medical degree was received from Marquette University.

He was active in professional circles and prominent as a speaker on medical subjects and other topics. For ten years he advised University of Minnesota School of Medicine graduates on "Medical Ethics and Medical Practice," and for many years participated in a speakers' panel sponsored by the medical school.

Dr. Hirschboeck was a former president of the St. Louis County Medical Society, the Minnesota Society of Internal Medicine, the Minnesota Branch of the American Heart Association, the Inter-Urban Academy of Medicine and the Minnesota Society of Diseases of the Heart and Circulation. He was also a member of the American Medical Association and the St. Louis County Medical Society and a Life and 50 Club Member of the Minnesota State Medical Association.

He is survived by two daughters and one son.

ELMER O. DAHL, M.D.

Dr. Elmer O. Dahl, 78, Minneapolis specialist, died November 5. A graduate of Loyola University, Dr. Dahl practiced medicine with his brother, Dr. John A. Dahl, in Minneapolis.

He was a member of the Hennepin County Medical Society, American Medical Association, American College of Ophthalmology and Otolaryngology and a 50 Club and Life Member of the Minnesota State Medical Association.

He is survived by his wife.

CARL J. T. LUND, M.D.

Dr. Carl J. Lund, 64, Fergus Falls physician, died October 16. Born in Saronville, Nebraska, he attended the University of Minnesota Medical School.

He was a member of the local school boards, the Lutheran Church of America, the Board of Gustavus Adolphus College, the American Medical Association, the Minnesota State Medical Association, and the Park Region District and County Medical Society.

He is survived by his wife, three daughters and two sons.

Admission Chest Film Program

Fifteen Years' Experience

L. M. HAMMAR, M.D.
Mankato, Minnesota

Is it justifiable to routinely x-ray the chest of every patient admitted to a general hospital? Is the information gained sufficiently valuable to warrant retention of the program? How productive is the study in detection of tuberculosis and other diseases? Have any serendipitous* effects accrued? What are the difficulties in administration of the program? These are the questions that need answers. Little has been published on the success or failure of the program in Minnesota since its inception in the early 1950s. It is hoped that analysis of our experience in a small general hospital (126 beds) may shed some light on the matter.

Background and Scope of the Program in Minnesota

On May 16, 1953, under the leadership of J. F. Briggs, M.D., and J. A. Meyers, M.D., the Council of the Minnesota State Medical Association recommended that a program of routine admission chest roentgenograms be instituted in all hospitals of the state. By 1965, 86% of the general hospitals in Minnesota required routine admission chest x-rays.[1] These hospitals admitted 549,550 patients or 91% of the patients entering general hospitals in Minnesota.

Instituting the Program

The policy of requiring an admission chest film was instituted at Immanuel Hospital, Mankato, Minnesota, in October, 1953. To make the program as inclusive as possible, no exceptions were permitted unless the patient had had a previous chest film within the last six months at either the hospital or the physician's office. Obstetrical patients were x-rayed as soon as possible after delivery. All others were filmed at the time of admission if their condition permitted. Many surgical patients at our hospital are admitted during the late afternoon; their chest films are taken at the time of the laboratory workup and interpretation is always available prior to surgery the next morning.

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*See Test Your Word Score Page 1921.

If an abnormality which would make anesthesia or a surgical procedure hazardous is detected, the surgeon is informed. Newborn infants are not routinely x-rayed. Very ill patients, some emergency cases and some transfers from other hospitals will occasionally be in the hospital for extended stays without admission films. In the 15 years covered by this report, there were 63,298 admissions and 36,475 admission chest roentgenograms.

Convincing the attending physician that his patient should have a routine admission chest film was sometimes difficult. "If I want my patient to have a chest x-ray, I'll order it." was the frequent objection. Cost to the patient was also mentioned. Unnecessary exposure to radiation, especially for obstetrical and pediatric patients, became frequent objections during the wave of apprehension concerning "fall-out" radiation in the late 1950s. Discussion of these problems at hospital staff meetings, programs showing actual cases benefited by admission chest roentgenograms, taking films of obstetrical patients after delivery, shielding gonadal regions in pediatric patients, all helped to overcome the objections. Cost to the patient was held to the lowest possible figure. Initially we charged $4.00 for a 14 × 17″ film; in 1964 the charged was increased to $5.00, and in 1968, to $6.00 for the examination.

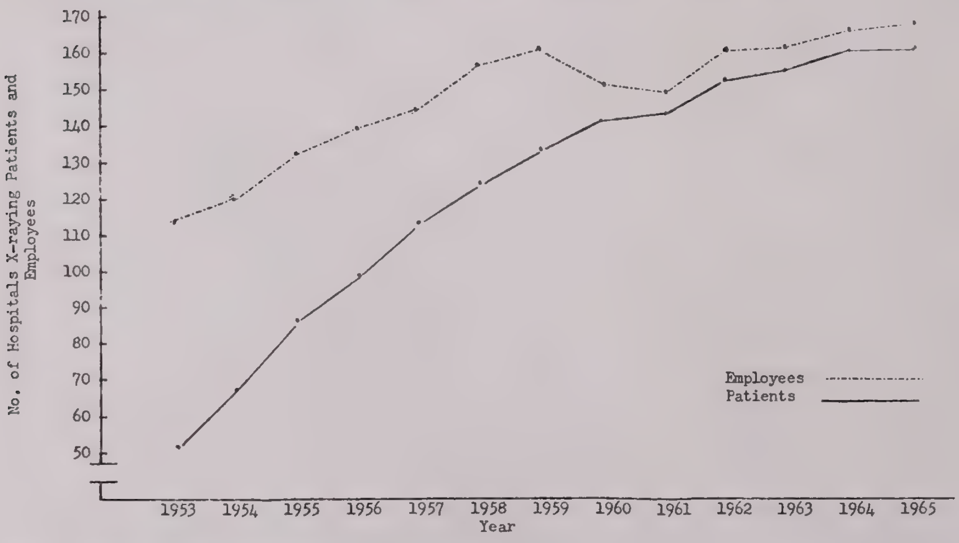
Results

The initial emphasis was on tuberculosis case finding. A high percentage of patients admitted to our type of hospital is in the geriatric range, and this segment of population is most apt to be harboring tuberculosis as a carry-over from the time it was much more prevalent. Review of our cases after the first 14 months (1635 admission films) showed discovery of one active case of pulmonary tuberculosis and seven inactive cases. With this start, we were encouraged to continue. Tabulation of other conditions revealed by admission chest films during the same initial period showed many serendipitous findings which further justified continuation of the program.

The accompanying table lists the most commonly encountered x-ray findings. Minor degrees of cardiac enlargement or early arteriosclerotic changes in the aorta were not listed

MINNESOTA DEPARTMENT OF HEALTH
Division of Hospital Services
March 1966

Progress of Programs in Admission Chest X-ray Examinations for Patients and Annual Chest X-ray Examinations for Employees in General Hospitals* in Minnesota from 1953 through 1965



Source: Hospital license applications submitted January 1, 1966

* Includes general hospitals and specialized units of general hospitals (except C & NC, nursing home, and boarding home units); does not include Federal hospitals, mental, tuberculosis, or chronic disease hospitals.

Figure

TABLE

Abnormalities Detected on Admission Chest Films

Condition	Times Found
Tuberculosis	
Active; cases not previously known	13
Inactive; old cases previously known	31
Suspected; not subsequently proven	23
Chest Conditions (non-tuberculous)	
Sarcoidosis	4
Pneumonia	355
Pneumonia in patients scheduled for surgery	16
Pleural effusion	23
Infarction	24
Abscess	4
Pneumothorax	5
Bronchial obstruction with lobar collapse	14
Foreign body (unsuspected)	3
Hilar adenopathy	42
Substernal thyroid	31
Mediastinal emphysema	1
Emphysema	19
Chest Conditions (neoplastic)	
Tumor in lung parenchyma (solitary)	39
Tumors, multiple, metastatic	61
Rib tumors	12
Mediastinal tumor	5
Heart and Aorta	
Pulmonary edema	4
Severe cardiomegaly	22
Arteriosclerotic heart disease	57
Heart and Aorta (continued)	
Mitral disease	17
Combined arteriosclerotic and mitral disease	11
Intra-cardiac calcification	2
Cor pulmonale	1
Pericardial calcification	1
Luetic aortitis	2
Aortic aneurysms	7
Pericardial effusion	3
Coarctation of aorta	2
Congestive heart failure	62
Anomalies	
Dextro-cardia	3
Right descending aorta	4
Cervical ribs	12
Funnel chest	2
Hepato-diaphragmatic interposition of colon	8
Atrial septal defect	1
Patent ductus arteriosus	1
Miscellaneous	
Myelofibrosis	1
Kyphoscoliosis (severe)	14
Subdiaphragmatic abscess	1
Fibrous dysplasia of rib	1
Air under diaphragm (unsuspected)	7
Diaphragmatic hernia	11
Addison's disease	2

or included in the table. A total of 1012 abnormalities was found in the 36,475 cases examined.

The table lists the most commonly encountered x-ray findings. Those listed as active tuberculosis were previously unrecognized cases, in which acid-fast organisms were seen in smears or demonstrated in cultures or guinea-pig innoculations. All but one of these active cases were over 50 years of age. The 31 inactive cases had all been diagnosed and treated previously, and pronounced arrested. The 23 listed as suspected but not subsequently proven cases had x-ray findings strongly resembling tuberculosis. Most of them received intensive study, including gastric washings and cultures. The remaining conditions listed in the table are x-ray diagnoses and most of them are self-explanatory. They were included only if reasonably clear-cut evidence was seen on the film, and if the condition was of possible clinical significance. Minor degrees of cardiac enlargement or early arteriosclerotic changes in the aorta were not listed. Many conditions seen on the films are not included in the table. A total of 1012 abnormalities was found in the 36,475 cases examined.

Comments

There is a small but significant segment of our older population still affected with active unknown tuberculosis. Sooner or later, most of these individuals are admitted to a hospital. The admission chest roentgenogram is an effective method of detecting these cases.

Transmission of tuberculosis to other hospital patients and especially to nurses may be circumvented.

Sixteen patients scheduled for surgery were found to have pneumonia or other pulmonary pathology contraindicating inhalation anesthesia.

Extra dividends from the program are the detection of numerous clinically significant and unsuspected conditions.

Reference

1. Report of Admission Chest X-ray Examination for Patients and Annual Chest X-ray Examinations for Employees, Minnesota Department of Health, March 1966.

Medical Terms and Their Lay Synonyms

(Continued from November issue*)

A

A dose—*gonorrhea*
A fling at cactus—*arsenical antisyphilitic treatment*
African sleeping sickness—*trypanosomiasis*
Afterbirth—*placenta*
Aftosa—*aphthous fever*
Ague—*malaria*
Ague cake—*chronic splenitis*
Ah ah boy—*physician*
Air bags—*lungs*
Air one's belly—*emesis*
Air pipe—*trachea*
Air tanks—*lungs*
Albumin in the urine—*toxemia of pregnancy*
Albuminuria—*nephritis*
Aleppe—*oriental sore*
Allantiasis—*botulism*
Alter—*castrate*
Althana—*anthrax*
Antitempest—*tetanus toxoid*
Aphroditis—*venereal disease*
Apoplexy—*cerebral stroke*
Apron—*omentum*
Are-ex—*prescription*
Arico vein—*varicose vein*
Arizona tenor—*tuberculous patient*
Armpit—*axilla*
Arse grapes—*hemorrhoids*
Arthritis—*gout*
Asian flu—*influenza*
Assmus—*astima*
Asturian leprosy—*pellagra and elephantiasis*
Athlete's foot—*tinea pedis*
Aurego—*icterus*
Australian Q fever—*Q fever*
Autoclave—*stomach*
Autumnal fever—*typhoid fever*
Autumnal catarrh—*hayfever*

B

Baby blow out—*delivery*
Baby bound—*pregnant*
Back cracker—*chiropractor*
Back raking—*digital removal of fecal impaction*
Backfire—*expel flatus*
Bacon—*human body*
Bad blood—*syphilis*
Bad breath—*halitosis*
Bag—*scrotum*
Bag of waters—*amnionic sac*
Baghdad boil—*oriental sore*
Baked tongue—*tongue of typhoid fever*
Baker's itch—*lichen chronicus simplex*
Baldness—*alopecia*
Ball bearings—*pills*
Ball in the throat—*globis hysterious*
Ballocks—*testicles*
Balls—*testicles*
Bang—*hypodermic injection*
Bang's disease—*brucella infection*
Banion—*epidermis*
Banjo—*bedpan*
Banyan—*epidermis*
Barbadof's leg—*elephantiasis*
Barber's itch—*sycosis*
Barcoo rot—*cutaneous diphtheria*
Barefoot dome—*alopecia*
Barf—*emesis*
Bark—*epidermis*
Barley skin—*xeroderma*
Barnacled—*wearing glasses*
Barrel chest—*emphysema*
Barrenness—*sterility*
Baseball finger—*fracture of distal phalaynx*
Basement—*abdomen*
Basket—*scrotum*
Basket sewer—*gastric ulcer*
Basket weavers—*psychiatry patients*
Bat's ears—*congenital forward angulation of the ears*
Bats in the belly—*nausea*
Bayonet leg—*posterior displacement of tibia and fibula*
Bay window pain—*abdominal pain*
Bazin—*Mulluscum contagiosum*
Be upholstered—*to be infected with venereal disease*
Beagle—*nose*
Bean—*brain*
Bean pad—*skull*
Bearing down—*pelvic heaviness*

Eugene Benet, M.D.†
Syracuse, New York

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*See page 1372.
†Assistant Professor of Radiology, University of Syracuse Medical Center.

Small Blood Vessel Syndrome

Constitutional Arterial Narrowing

THOMAS E. JOHNSON, M.D.*
St. Paul, Minnesota

THE GRADING OF PERIPHERAL PULSES is a necessary part of all physical examinations. It provides a base line reference for the future as well as an estimation of the current status of a patient's blood vessel health. For the angiographer a pre-angiographic record of the peripheral pulses is mandatory. An estimation of the blood vessel size and possible anatomical variations to be encountered can provide for fast, safe and accurate diagnosis during subsequent angiography.

Young female adults are known by angiographers to possess small, elastic blood vessels. Patients with short stature and mild truncal obesity have an even greater degree of constitutional narrowing as well as a frequent important anatomical variation of the common femoral artery. This narrowing predisposes them to symptomatic occlusive disease at an early age.

The Material

In an analysis of 21 exemplary patients, 14 were under 50 years of age; eight of 14 suffered from symptomatic occlusive disease; seven required surgical corrective procedures; four were less than 41 years of age. Average height and weight was five feet, two inches and 124 pounds.

The Findings

Without correction for magnification as produced by x-ray projection, average measurement of the aorta-ilio-femoral lumen in these patients is listed (Table 1), and illustrated in the composite (Figure 1). They have a normal-diameter lower dorsal aorta,[1,2] however; a comparison with Steinberg's[1] 500 patients reveals an exaggerated tapering of the caudal aorta below the renal arteries in constitutional narrowing. Major extremity arteries have a similar reduction in size not due to atrophy secondary to proximal stenosis. An average normal patient has a common femoral

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*Department of Radiology, The Charles T. Miller Hospital, St. Paul, Minnesota.

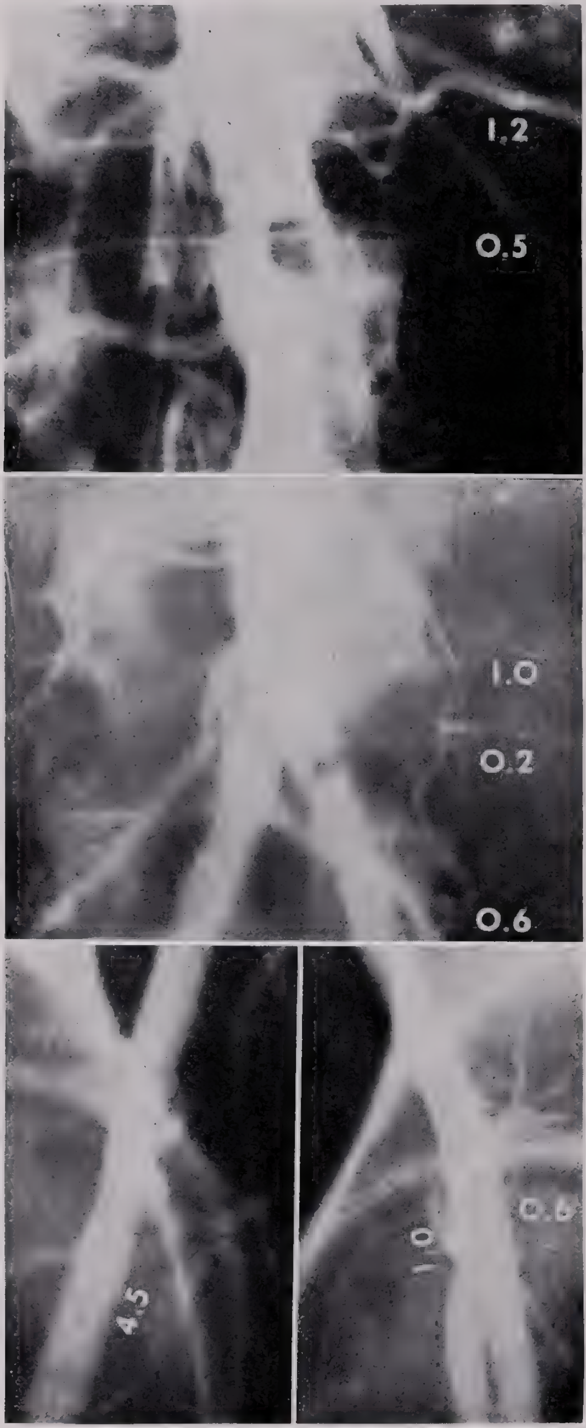

Fig. 1—Composite Film of Three Patients

(Top) Aorta: 0.7cm. plaque in 1.2cm. lumen
(Middle) Iliac artery: 0.4cm. polyp-like atheroma in a 0.6cm., otherwise normal lumen on the left side.
(Bottom) Right femoral artery: 0.6 × 4.5cm.
Left femoral artery: 0.6 × 1.0cm.
Superficial femoral artery: 0.4cm. wide

artery which is 1.0 cm wide and 6.0 cm long.

TABLE I

	Steinberg-Normal Aorta (±0.3 cm)	Constitutional Narrowing Average
At T-12	2.44 cm	2.0 cm
Above renal arteries	2.16 cm	1.8 cm
Below renal arteries	1.87 cm	1.5 cm
At bifurcation	1.75 cm	1.2 cm
Common femoral		0.6 cm × 3.0 cm
Popliteal		0.35 cm

Literature

Wertheimer[3] has theorized that congenital narrowing of vessels results in a secondary increase in peripheral resistance giving rise to intimal thickening and thrombosis on the same basis as in primary or secondary pulmonary hypertension. Clemetson[4] has reviewed a possible correlation of pre-eclamptic toxemia of pregnancy with the presence of a small abdominal aorta in five of eight patients. All were less than five feet three inches tall and had mild truncal obesity. Hypertension was not a frequent finding in any of our 21 cases and, when present, was explained with one exception by renal artery stenosis or occlusion or chronic pyelonephritis. Obstetrical histories in four patients were normal and not obtained in the rest.

It would be misleading to describe these patients as having aortic hypoplasia.* Most such cases are associated with abdominal coarctation, tubular hypoplasia, supravalvular aortic stenosis or other complicated congenital cardiovascular problems. The small vessel syndrome is commonplace, whereas a true hypoplasia is a rarity as shown by Ikeda's discovery of eight cases in 14,000 autopsies.[6]

Significance

A frequent erroneous downgrading of peripheral pulses is observed in these patients. This is due to a combination of the following factors: (1) a short narrow common femoral artery; (2) high bifurcation of the common femoral artery; (3) tiny anterior and posterior tibial arteries.

In one half of these patients the common femoral artery was less than 3 cm long. Digital examination in the usual location therefore causes one to palpate the smaller superficial femoral artery instead of the common femoral artery in the groin. This can give the examiner the false impression that the femoral pulse is diminished over expected. The bifurcation anomaly is not always bilateral; therefore one femoral pulsation may seem diminished to palpation as compared to the other, or both may seem of abnormally low amplitude when in fact both are normal for the size of vessel present. Palpation must be done high in the groin, close to the inguinal ligament.

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*See Test Your Word Score Page 1921.

The tibial arteries, although adequate for the patient, can be the size of a small thread and may be very difficult to feel at the ankles. A very delicate palpating touch is necessary for accurate peripheral pulse grading. Several patients herein reported have had angiographic examinations because of vague leg symptoms or varicosities and "absence" or "diminution" in one or more of the ankle pulses; therefore arterial occlusive disease was suggested where none existed.

The ankle pulses must be checked throughout the examination. In addition, these small vessels have a strong tendency to go into spasm, either at the needle puncture site or around the catheter. This spasm may be located at the femoral insertion site, but we have also observed severe pericatheter spasm of the entire iliac artery.

It is desirable to use heparinized saline for catheter flushing even though one is not performing an examination above the diaphragm.

Catheters which are formed for selective arteriograms of various body organs must be made with a much smaller curve at the tip since these small aortas will hold the tip straight and not allow it to curve into the desired course. The catheters themselves should have the smallest outside diameter consistent with a diagnostic examination.

The most important point is the fact that a very small amount of atheromatous tissue can produce a very significant constriction of the lumen of these vessels; therefore these patients tend to become symptomatic while disease is well localized and minimal in nature. As mentioned, eight patients had symptomatic occlusive disease before 50 years of age. One should keep in mind that young females with this body habitus who have vague or even typical symptoms of extremity ischemia should not be ignored because of their age and sex. Close appraisal of these symptoms should be made along with the peripheral pulse examination.

When the more severe form of small abdominal aorta or iliac artery is encountered with localized atheromatous partial occlusion, one should consider an aorto-iliac replacement by prosthesis rather than localized endarterectomy. Two of these patients who underwent abdominal aorta endarterectomy required repeat surgery within two years of the original operation, due to progression in size of small atheromatous deposits elsewhere between the renal arteries and the aortic bifurcation (Figure 1).

Summary

Short female patients who have mild truncal obesity show a significant incidence of constitutional arterial narrowing. This can be normal for a given patient but predisposes her to symptomatic degenerative disease at an early age. It is frequently associated with high bifurcation of the common femoral artery, diminutive ankle pulses and a definite tendency for spasm secondary to direct trauma by needle or catheter. During the physical examination, recognition of these patients is possible with a fairly high degree of accuracy. Erroneous conclusions regarding the adequacy of peripheral pulsations can thus be prevented.

When angiographic diagnosis is necessary, the size of the arterial tree and the anatomical pattern to be encountered are predictable, thus allowing the selection of appropriate instruments, puncture site, and catheter form. Unnecessary catheter exchanges and superficial femoral artery obstruction during arteriography can be prevented. In some instances, aorto-femoral bypass graft is preferable to limited aortic endarterectomy even though the disease is limited to a small segment of the aorta or iliac artery.

References may be secured from the author or the reprints.

Many a family tree needs trimming.—Frank Hubbard

Meetings and Announcements

American Board of Family Practice

The American Board of Family Practice announces that it will give its FIRST examination for certification in various centers throughout the United States. The examination will be over a two-day period on February 28-March 1, 1970. Information regarding the examination and eligibility for the examination can be obtained by writing: Nicholas J. Pisacano, M.D., Secretary, University of Kentucky Medical Center, Annex #2, Room 229, Lexington, Kentucky 40506.

Clinical Neurology Fellowships

Fellowships in Clinical Neurology have been established at the Minneapolis Veterans Administration Hospital.

General Practitioners and Non-Neurological Specialists are invited to apply for an intensive postgraduate training experience on the Neurological Wards at the Minneapolis VA Hospital. Programs are designed to provide one to four weeks of supervised bedside and didactic instruction in the diagnosis and treatment of neurological disease. Those accepted for the fellowship may receive quarters, if desired. Fellows may elect any one or a combination of the following programs:

Week 1—The Neurological Examination
Week 2—Special Neurological Diagnostic Procedures
Week 3—Latest Treatments of Acute and Chronic Neurological Problems
Week 4—Frontiers of Neurological Research

Each program will commence on Monday and terminate on Friday.

Apply to Milton Alter, M.D., Ph.D., Chief, Neurology Service, Veterans Administration Hospital, 54th St. and 48th Ave. So., Minneapolis, Minnesota 55417.

Minnesota Heart Association

Heart symposium, Saturday and Sunday, January 24-25, sponsored by the Minnesota Heart Association at the St. Paul Hilton Hotel, St. Paul, Minnesota. Topic: What To Do About High Blood Pressure? Chairman: Kenneth G. Berge, M.D.; Time: January 24th, 8:30 to 4:30 and January 25th, 9:00 to 12:00.

February Meetings

Hennepin County Academy of General Practice Chapter Meeting, February 16 at the Minneapolis Athletic Club.

Minnesota Academy of Occupational Medicine and Surgery, February 19th at the Minneapolis Club, 729 Second Avenue South, Minneapolis, Minnesota. Program Chairman: Edwin G. Benjamin, M.D.

Don't knock the weather; nine tenths of the people couldn't start a conversation if it didn't change once in a while.—Frank Hubbard

Inner Sites...

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Blood and urine: therapeutic antibacterial levels within 2 hours for up to 12 hours

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The mucosa: specific analgesia usually within 30 minutes

Azo (phenazopyridine HCl) effects specific mucosal analgesia, relieving the dysuria, discomfort and burning which are virtually always a part of acute urinary tract infections.

Interstitial fluids: ready diffusion of antibacterial

Gantanol (sulfamethoxazole) is readily diffused into interstitial fluids to provide efficient antibacterial activity at foci of infection. This distribution, plus continuous antibacterial levels in blood and urine, has afforded effectiveness in the majority of infections in which it has been used.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Urinary tract infections with associated pain or discomfort when due to susceptible organisms; prophylactically in urologic surgery, catheterization and instrumentation.

Contraindicated in sulfonamide-sensitive patients, pregnant females at term, premature infants, newborn infants during the first three months of life, glomerular nephritis, severe hepatitis, uremia and pyelonephritis of pregnancy with gastrointestinal disturbances.

Warnings: Use only after critical appraisal in patients with liver damage, renal damage, urinary obstruction or blood dyscrasias. If toxic or hypersensitivity reactions or blood dyscrasias occur, discontinue therapy. In closely intermittent or prolonged therapy, blood counts and liver and kidney function tests should be performed.

Precautions: Observe usual sulfonamide therapy precautions including maintenance of an adequate fluid intake. Use with caution in patients with histories of allergies and/or asthma. Patients with impaired renal function should be followed closely since renal impairment may cause excessive drug accumulation. Occasional failures may occur due to resistant microorganisms. Not effective in virus and rickettsial infections.

Adverse Reactions: Headache, nausea, vomiting, urticaria, diarrhea, hepatitis, pancreatitis, blood dyscrasias, neuropathy, drug fever, skin rash, Stevens-Johnson syndrome, injection of the conjunctiva and sclera, petechiae, purpura, hematuria or crystalluria may occur, in which case the dosage should be decreased or the drug withdrawn.

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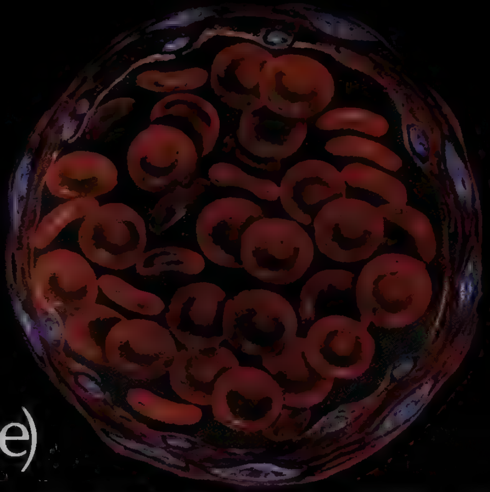
Azo Gantanol®

(Each tablet contains 0.5 Gm sulfamethoxazole and 100 mg phenazopyridine HCl.)



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(nicotinyl alcohol tartrate)

Because peripheral vasodilation is needed now... and must often be continued

Roniacol Timespan (nicotinyl alcohol tartrate) can make a significant contribution to effective treatment of peripheral vascular disorders. It is directed specifically toward improvement of peripheral blood flow, relief of ischemic symptoms, and the long-term management of these conditions.

Specific pharmacologic action—Roniacol (nicotinyl alcohol) acts selectively by relaxing smooth muscle of peripheral blood vessels. Onset of action is smooth and gradual, rarely causing severe flushing.

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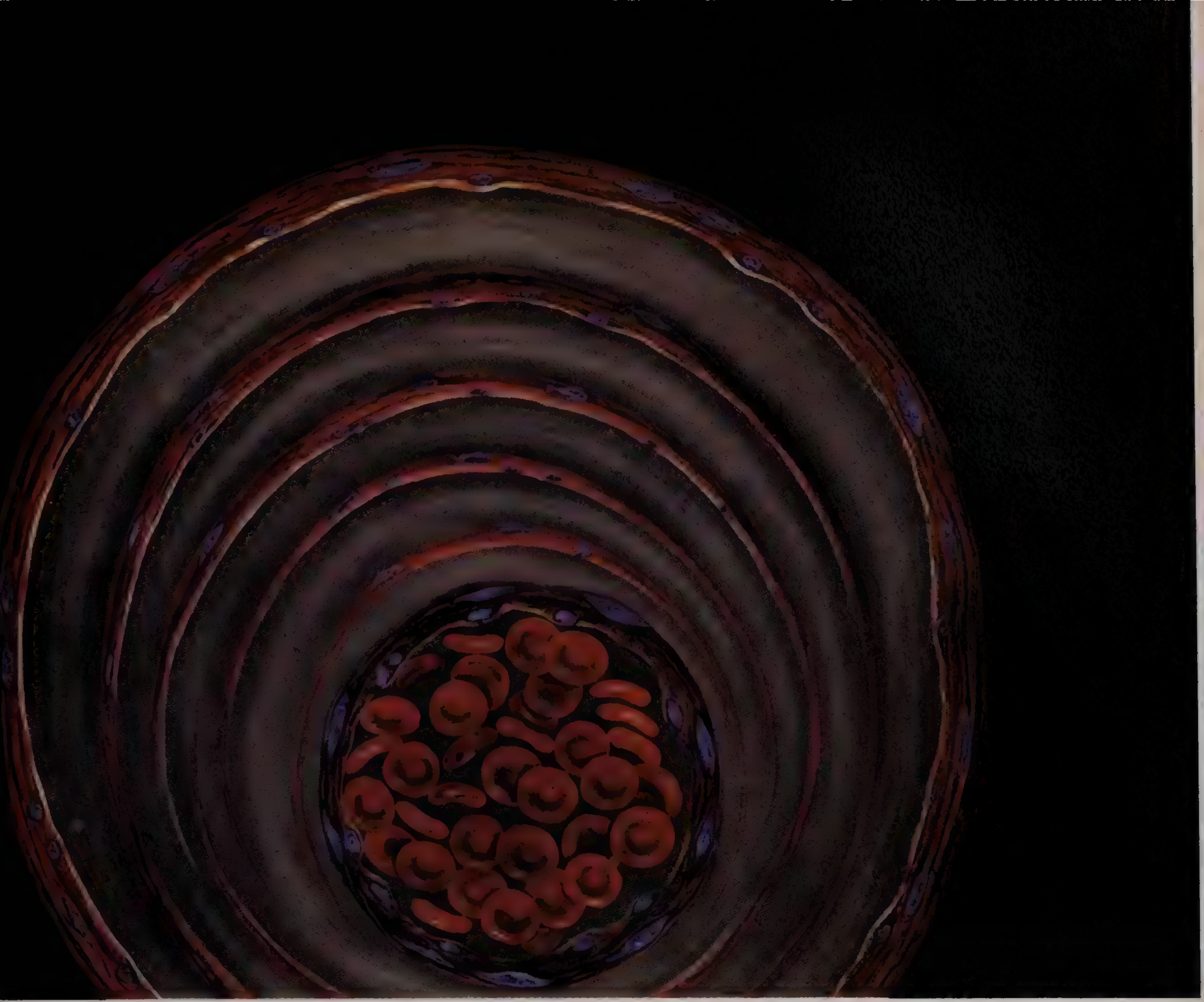
Prolonged, continuous drug release—Prolonged peripheral vasodilation is provided by sustained-release Roniacol Timespan (nicotiny alcohol tartrate) Tablets. Part of the drug becomes available immediately, the remainder continuously over a period of up to 12 hours, and dilation of constricted peripheral vessels i usually maintained. Thus, with a single dose o medication, patients can enjoy the benefits of increased peripheral blood flow in ischemic extremities for up to 12 hours.



Smooth peripheral vasodilation from initial dosage...extended with simple, well-tolerated, b.i.d. dosage

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Before prescribing, please consult complete product information, a summary of which follows:

ndications: Conditions associated with deficient circulation; e.g., peripheral vascular disease, vascular spasm, varicose ulcers, decubital ulcers, chilblains, Meniere's syndrome and vertigo.

Caution: Roche Laboratories endorses caution in the administration of any therapeutic agent to pregnant patients.

Side Effects: Transient flushing, gastric disturbances, minor skin rashes and allergies may occur in some patients, seldom requiring discontinuation of the drug.

Dosage: 1 or 2 Timespan Tablets—150 mg nicotinyl alcohol in the form of the tartrate salt—bottles of 50 and 500.

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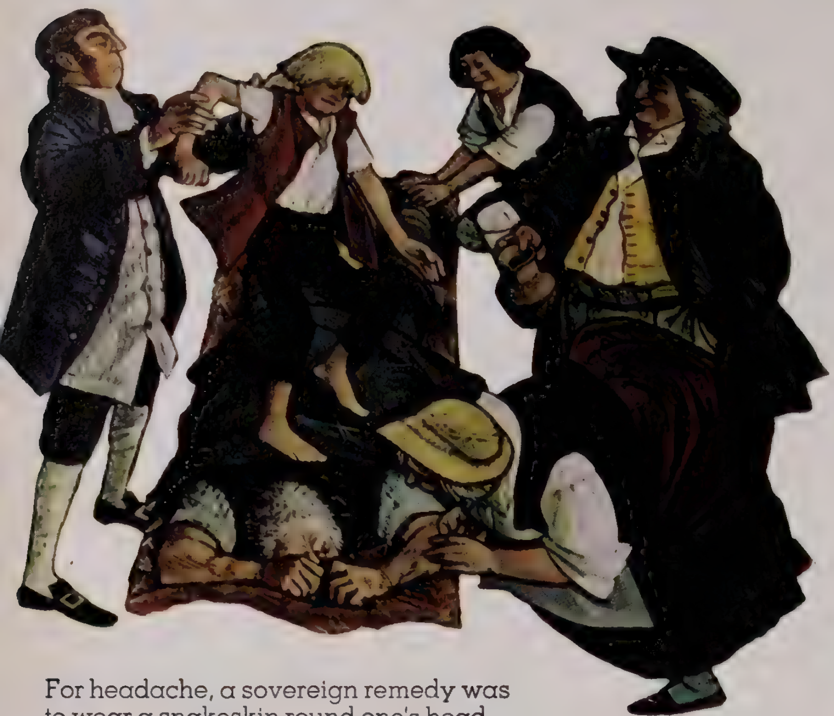
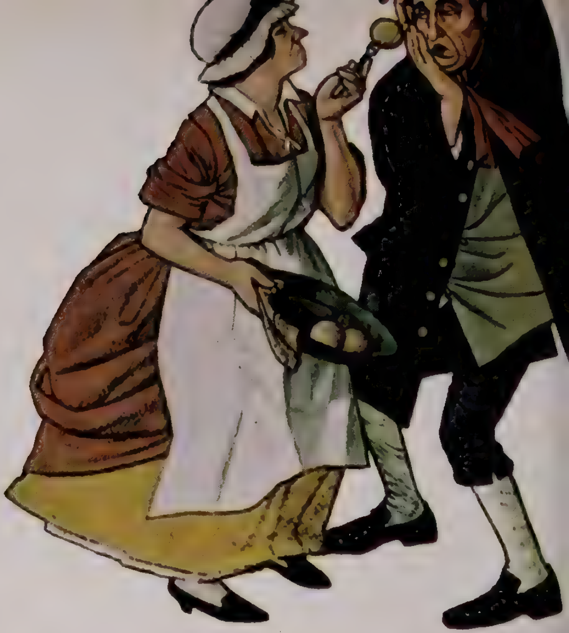
Nutley, New Jersey 07110

Art is a conception of peripheral vasodilation.

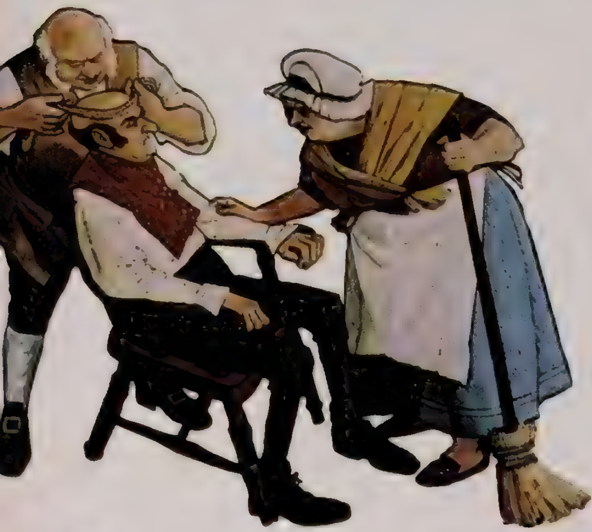
A once-popular treatment for back pains was to have the seventh son of a seventh son stand or walk on the patient's back.





The pain of earache was allegedly relieved by holding a hot roasted onion to the ear.

For headache, a sovereign remedy was to wear a snakeskin round one's head.



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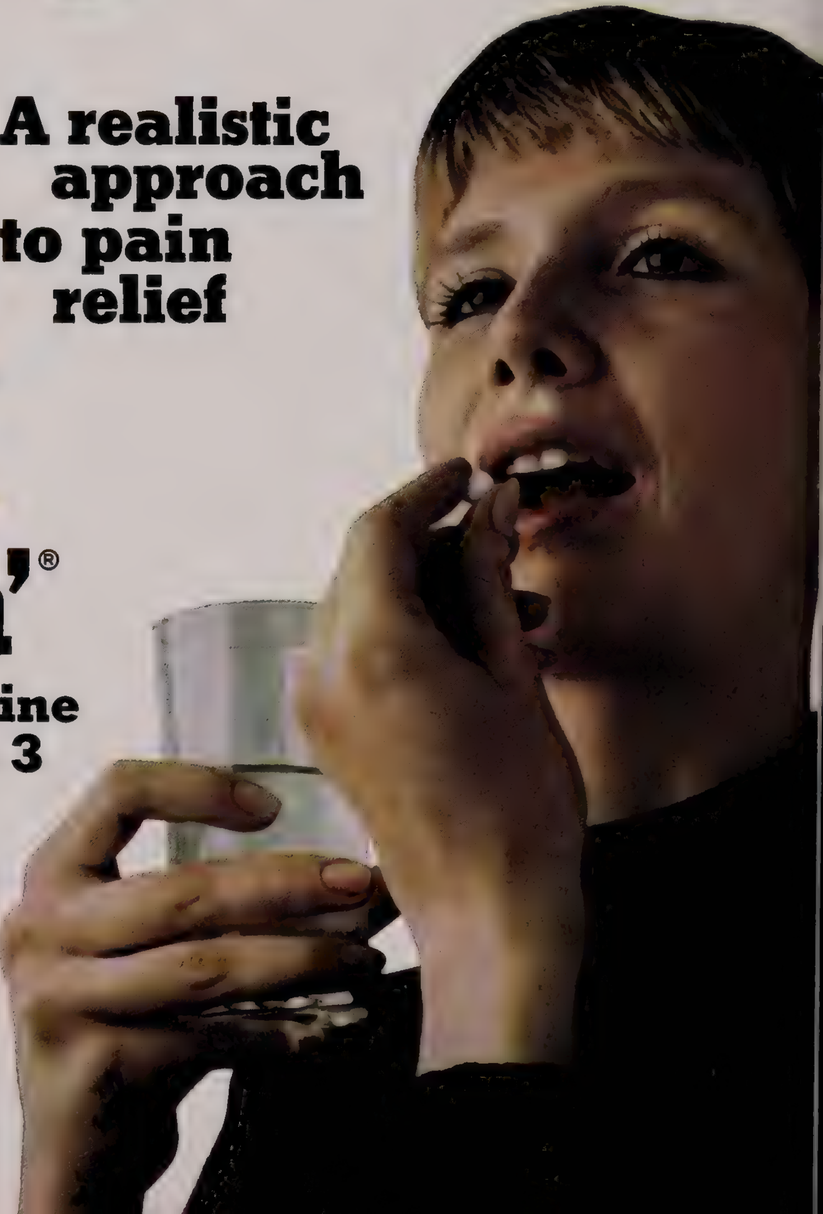

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Editorials

The First Time

This is the first time that Members of the Minnesota Radiological Society pool their works in a single issue of Minnesota Medicine. The result is an eloquent illustration of the scope and depth of the specialty of Radiology.

This collection of articles is also a fitting tribute to an eminent radiologist and a much respected teacher, Dr. Harold O. Peterson, himself a contributor to this issue.

Thanks are due the Editorial Staff of Minnesota Medicine for their help and cooperation, and the members and officials of the Society for their enthusiasm and support.

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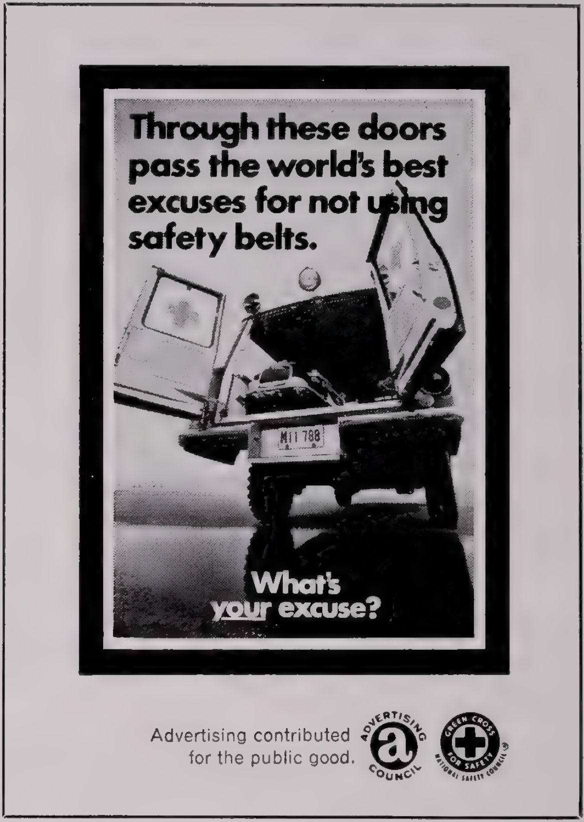
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Radiology

Responsibilities and Opportunities

Within the past decade, radiology has gained increasing importance and stature within the medical community.* There are today in the United States approximately 8,000 radiologists. The recent report of the National Advisory Committee on Radiation estimates that by 1975 this country will need 25,000 practicing specialists in radiology.

The responsibilities and opportunities of a University Department of Radiology lie in undergraduate education, graduate training, and fulfillment of community needs.

Not many years ago, most residents were older practicing physicians; today they are medical students. The choice of radiology as a career was often related to the lessened physical demands upon the individual as compared with other clinical disciplines. Today this is no longer true. The growth of angiography has contributed much to this change, but we must also credit the increase in knowledge gained from the basic sciences and various clinical specialties. The academic Department of Radiology must offer a strong undergraduate teaching program, not only to attract good people, but also to instruct the future practitioner where and how radiology may aid in the diagnosis and treatment of his patients.

In a sense, every radiologist is a teacher. Increasingly, radiology is a hospital base specialty, and the physician on his daily rounds seeks the aid and advice of the radiologist. The demand for community radiologists creates an even more pressing need for astute teachers and investigators. An academic department must offer opportunities for basic and clinical research; an atmosphere where inquiry is encouraged. Furthermore, increased knowledge in all areas of radiology has stimulated the development of subspecialties such as neuroradiology, cardiovascular radiology, and pediatric radiology.

The shortage of radiologists requiring specialized training is attaining alarming proportions. It is evident that in order to fulfill our responsibility we will have to not only train more radiologists but also develop better methods of utilization of these valued specialists. Reevaluation of the classical methods of radiological practice, better use of technicians by offering specialized training in areas which were until now considered strictly within the scope of the radiologist, and analysis of technological advances are all under study.

In order to meet the need, the University of Minnesota Integrated Residency Program in Radiology is at present training 65 radiologists, by far the nation's largest radiology residency program; and to further combat the shortage, close affiliation is being developed with other hospitals in the community interested in undergraduate and postgraduate training. The Minneapolis Veterans Administration hospital, Hennepin County General Hospital, and St. Paul-Ramsey Hospital already form an integral part of this program. Additional affiliations, where such affiliation is of mutual interest and benefit, are being sought. Furthermore, it is our feeling that members of the local radiological community, can and should participate actively in the graduate training program. At present, over 40 radiologists in the Twin Cities area hold clinical staff appointments in this department.

In 1937, under the guidance of Dr. Leo G. Rigler, this department established the first postgraduate continuation course in radiology in the nation. This course has been held each fall for over 30 years, always attracting a large enrollment from all parts of the United States and Canada. The University is in a position to develop this area of continuing education even further. One area presently being explored would be allowing practicing radiologists to return on a voluntary basis to the academic center periodically to learn new techniques and update their knowledge. It may even be possible to provide reasonable coverage (probably in the form of adequately trained residents) to permit the practicing radiologist time away from his practice to participate in such activities This continuing education

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*John Knowles: New Engl J Med, page 1271, June 5, 1969.

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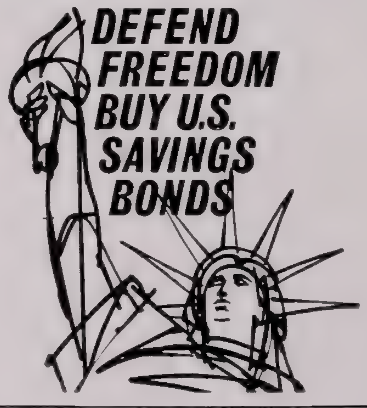

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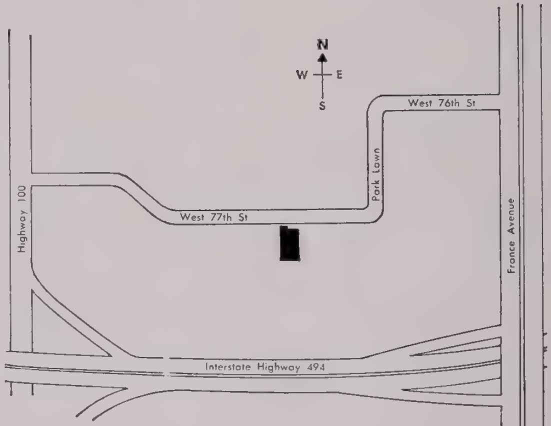

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should encompass not only diagnostic radiology and its various subspecialties, but also the fields of nuclear medicine and radiation therapy. Similar courses could be developed for radiologic technicians. Support for these undertakings could reasonably be expected from regional medical programs. These activities offer the possibility of improving not only the quality of radiology but also the relationships between the University and the private sector of radiology, for it is my opinion that these lines of communication should and must be improved.

Where knowledge is weak, prejudice often becomes strong. Academic radiologists must never become blind to the needs of the community. On the other hand, the practicing radiologist should not only recognize the nature and responsibilities of academic radiology, but wherever possible aid us in our tasks. If we act from a position of mutual respect and understanding, both the University and the community will benefit. Together, the proud heritage of Minnesota Radiology will be preserved and the challenges of the future will be met.

E. Gedgaudas, M.D.*
Minneapolis, Minnesota

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*Professor and Head Department of Radiology, University of Minnesota Hospitals.

Eugene Gedgaudas, M.D.

Dr. Eugene Gedgaudas, who succeeds Dr. Harold O. Peterson as Head of the Department of Radiology at the University of Minnesota, was born in Lithuania and received his premedical education in Lithuania before entering medical school in Germany, graduating from the University of Munich in 1948. He took his training in radiology in Canada and at the University of Minnesota.

Joining the full-time staff of the University in 1963, he became Head of the Department of Radiology on October 1, 1969. He is the third man to head the department since it was established in 1935. Dr. Leo G. Rigler headed the Division of Radiology in 1927 and in 1935 was made Chief of the Department.

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References: 1. Jaffe, J. H.: in Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, 3rd ed., 1965, pp. 279-280. 2. Woods, L. A., in Drill, V. A.: Pharmacology in Medicine, 1958, pp. 226-227. 3. Goth, A.: Medical Pharmacology, 2nd ed., 1964, pp. 336-337. 4. Beckman, H.: Pharmacology, 2nd ed., 1961, pp. 180-183. 5. LaBrecque, D. C.: Curr. Ther. Res. *8*: 106-109, 1966. 6. Dunlop, E.: J. Amer. Geriat. Soc. *16*:343-349, 1968.

Subspecialization in Radiology

In the years since the end of World War II, the field of radiology has undergone a complete transformation. The radiologist today is better able to delineate pathology because of improved technology (image intensifiers, television, rapid film changers) and the advent of angiography and other special procedures.

As a result, there has been within this last quarter century a tremendous advancement of knowledge within the field of radiology. The radiologist, generally working in close collaboration with clinical and basic science colleagues, has defined a whole host of radiographic patterns of disease. This burgeoning of knowledge has been due in no small measure to the activities of radiologists who have developed areas of special interest. Generally, such individuals have been working in large academic centers, but by no means is this always the case; radiologists working in community hospitals have contributed much, for example, to the development and improvement of angiography. It is not unreasonable to say that a person interested and engaged in a particular area of radiology becomes more competent in that area than another individual who does or attempts to do the entire gamut of this broad and diverse specialty. In fact, it is probably fair to state that today there can no longer be such a thing as a complete radiologist.[1] Therapeutic radiology is presently in the process of establishing itself as an independent though closely related specialty; such separation is already complete in Canada, Great Britain, and continental Europe. Fairly well defined subspecialty areas of pediatric, neurocardiovascular, gastroenterologic, uro-, and even chest radiology will likely evolve in the next decade. These subspecialties will, of course, only reflect advancement in medical knowledge and practice.

Clinicians trained in medical and surgical specialties in large teaching centers have become accustomed to working with proficient radiologic subspecialists in their areas during residency. Competent radiologic aid and consultation should and can be available to these individuals when they enter private practice.[2] It is to this end that almost every large teaching department of radiology is vigorously pursuing the development of subspecialty training.

It has been argued that the economics of the private practice of radiology are in conflict with subspecialization. While this may have been true in an earlier era when radiologists practiced solo and the specialty was based more in the office than in the hospital, it is probably much less true today. A large part of radiology today is hospital based, and groups of three or more radiologists in hospital practice are more the rule than the exception. Most of these groups have one or more radiologists with a special competence in the area of angiography. It is not unreasonable to expect that in the near future, individuals with special competence in neuroradiology and pediatric radiology will be found in these groups.

The American Board of Radiology is presently engaged in a study of this trend toward subspecialization.[3] It is likely that the future trainee in diagnostic radiology will receive a core curriculum of approximately two years' length in radiologic basics. Following this, he will take an additional one and one half to two years of subspecialty training. This is not to imply a bleak future for general diagnostic roentgenology; in fact, we can expect that the majority of trainees will opt for and be needed in the practice of the entire field, but that their last two years of training will likely be composed of rotations through the various subspecialty training programs. The greater emphasis on subspecialization will undoubtedly result in better teaching of the general diagnostic radiologist as well as the individual who chooses a special field of competence.

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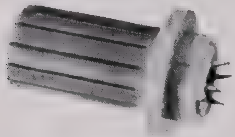

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any part of this nation and doubtless will be a leader in the trend to subspecialization.

Stephen A. Kieffer, M.D.*
Minneapolis, Minnesota

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*Associate Professor of Radiology, University of Minnesota and Chief, Radiology Service, Veterans Administration Hospital.

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1. Baker, D. H.: Pediatric Radiology: The First Decade—The Second Decade? Amer J Roentgenol 103:224-225, 1968 (May).
2. Holman, C. B.: The Availability of Neuroradiology. Amer J Roentgenol, 104:231, 1968.
3. Van Epps, E., in Debate: Should There Be Subspecialty Boards within Diagnostic Radiology. 1969 Conference of Teachers of Radiology. Chicago, American College of Radiology, pp. 86-95, 1969.

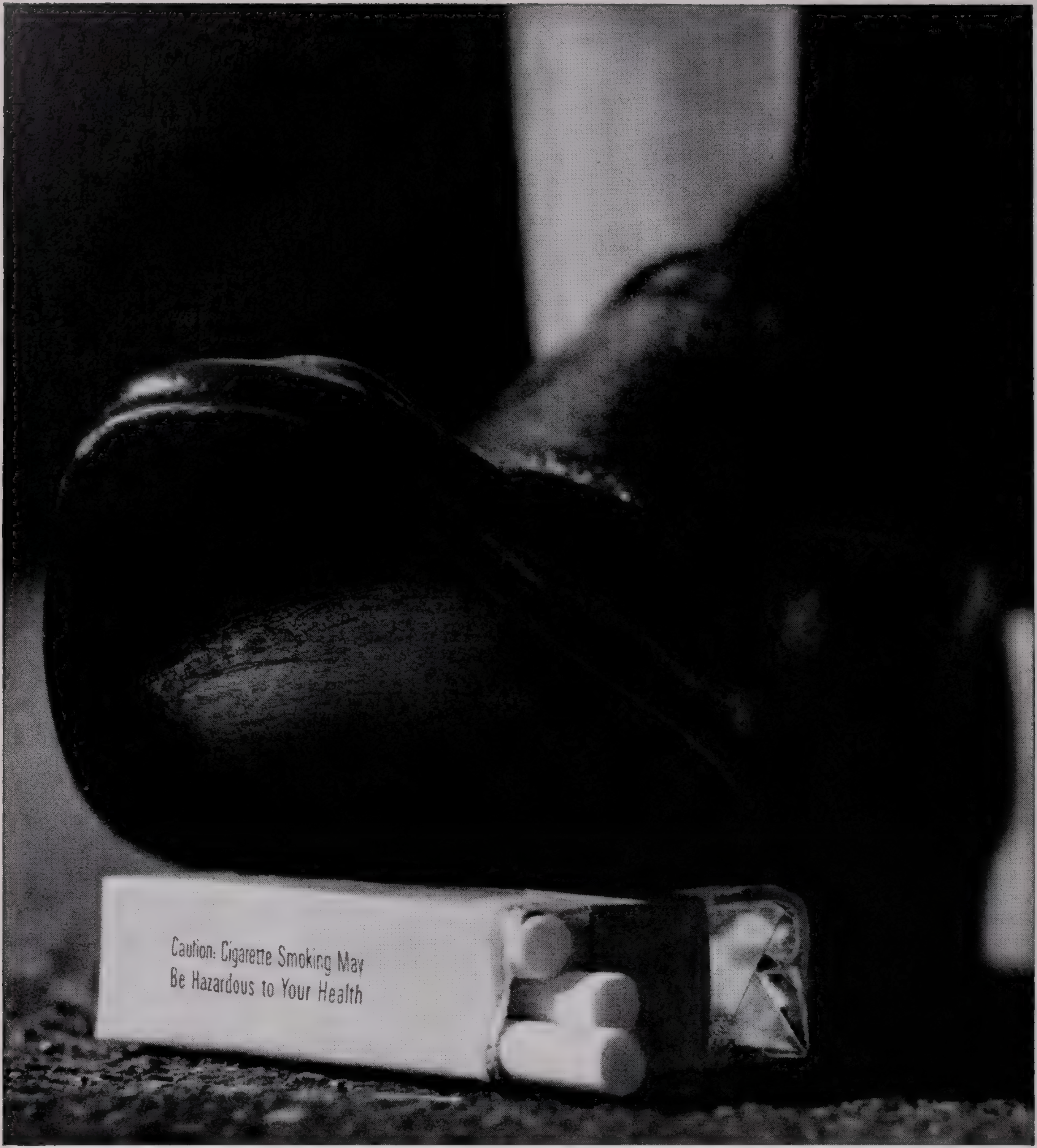
Radiology

THIS ISSUE OF MINNESOTA MEDICINE celebrates the science of radiology in general and extolls one of its brilliant exponents in particular, Dr. Harold O. Peterson, on the occasion of his retirement as Chief of the Department of Radiology at the University of Minnesota. The entire history of radiology in Minnesota is encompassed by the careers of Peterson and his predecessor, Leo Rigler, who as a student witnessed the infancy of the specialty. There are several tributes to Harold Peterson in this issue one of which is from Dr. Rigler; but Rigler's greatest tribute occurred twelve or thirteen years ago when he recommended Peterson to succeed him to the throne of radiology. Today the reasons for that recommendation are apparent to all. The State of Minnesota and particularly its medical citizens are proud of the achievements of Harold Peterson, this native son, who grew to greatness in our midst. He has contributed vastly to the advancement of his specialty; as professor he has taught not only residents numbered in hundreds and students counted in thousands, but the whole world of radiology through his papers and courses. His particular interest in radiology is its application to neurology.

In the era of Rigler and Peterson the great advances in radiology were achieved in part by discoveries of new methods of delineating structure either by opacification or increasing radiolucency, at the same time increasing the source of energy (and other methods), cutting the time of exposure and so culminating in the art of cineradiography. Thus the diagnosis of heart and great vessel disease has been illuminated by angiography. But now the whole methodology of the art of visualizing the hidden organs of the body is in flux. One method produces organ pictures on x-ray film, eliminating the x-ray machine entirely (but not the radiologist!). I refer of course to radioscanning which until recently has been hampered by the cumbersome ox in the field boustrophedonic technic. Employing the Anger camera revolutionizes the method by cutting the exposure time from a large fraction of an hour to a mere fraction of a second.

To hazard a guess about the post-Peterson decade; the seventies should witness great advances in radiology by application of this method. Radiologists have been most ingenious in contorting the human body to line part of it up with an x-ray tube, and a piece of film, so that now half their problem is solved, by rendering that body part temporarily radioactive. A previously impossible view, for instance, a vertical skull picture of the top of the head, will be commonplace. But whatever the advances of the seventies, Harold Peterson will be in the midst of them, for though he is retiring as head of the department of radiology at the University, he is still a young man who will continue to contribute to his field for many years to come. This prediction is well founded in precedent, recognizing what Leo Rigler has continued to accomplish after his retirement.

Reuben Berman, M.D.
Associate Editor
MINNESOTA MEDICINE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Test Your Word Score

Menarche—*the establishment of the menstrual function* (page 1859).

Phenotype—*a type determined by the visible characters common to a group as distinguished from their hereditary character* (page 1860).

Synarthrosis—*an immovable articulation in which the bones are united by intervening fibrous connective tissues* (page 1861).

Dysostosis—*defective ossification* (page 1863).

Potsherd—*a shard of broken pot* (page 1864).

Dosimetry—*the accurate determination of dosage* (page 1869).

Serendipitous—*the gift of finding valuable things not sought* (page 1899).

Hypoplasia—*incomplete development of a part* (page 1904).

Treponemal—*characterized by Treponema: a genus of schizomycetes, made up of parasitic and pathogenic spiral microorganisms* (page 1935).

Old Hospitals

(Continued from page 1872)

The new hospital, completed in 1734, was a one-story brick building, 34 x 90 feet, with a hipped roof in the formal French style of Louis XV. It consisted of a single large room with a fireplace at the far end flanked by windows. Entrances were provided in the center of each of the long sides and at the end adjoining the convent. The floor was tiled and the windows glazed.

The need for room to house "ancillary services" resulted in construction of several additions; the proposed plan for one to include a pharmacy, laboratory and quarters for surgeon and chaplain is shown. By 1752, there were 120 patients in the hospital.

The hospital and its additions were included in the inventory of public buildings of 1766 when Louisiana was transferred to Spain. The Spanish continued to use the facility as a military hospital, and added a second story to the main building. When the United States took possession of Louisiana, the Ursulines acquired title to the hospital, and in 1821 they had it demolished. Today nothing remains of the hospital with the possible exception of part of an old building near present-day Decatur and Governor Nicholls Streets on which can be seen a bit of stucco cornice which may have been part of the old hospital* laboratory.

Warren L. Kump, M.D.†
Minneapolis, Minnesota

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*The Louisiana Historical Quarterly, 29, 559, 1946.
Wilson, Samuel, Jr., New Orleans, personal communication.

†Secretary, Minnesota Radiological Society.

You May Be Right

Canned Consultation*

Day or night, Monday through Sunday, physicians in this state with a problem patient feel free to and do call consultants of their choice about specific problems. The salutation "Hi" is a warm one for both parties since they have developed a closeness formed of mutual respect due to repeated contacts concerning the welfare of their patients. The closing amenities reflect the same feeling because of shared knowledge and help.

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Then there was an instance when a physician used Dial Access to check his management of a particular patient. Immediately thereafter he placed a call to his consulting neurosurgeon and this patient was referred for a brain scan and change in management.

The Point? Those physicians who feel Dial Access replaces consultation or even postgraduate study are doing themselves and their patients a disservice. Those physicians who use Dial Access to enhance their knowledge are increasing their ability to care for patients.

Practitioners if you feel federal money should be spent under local control to improve medical care for the population, dial 800—356-8103 and learn something. Consultants, if you feel inclined to share your expertise for the improvement of medical care in Minnesota, dial 612—224-4771 and offer your services.

George B. Martin, M.D.
Thief River Falls, Minnesota

The Minnesota Medicine issue containing your delightful editorial "Canned Consultation"* just landed on my desk. You're right about consultation, of course. It is a human act, not instant information retrieved over the phone from a taped voice. The physician's mind is not a container to be filled with facts, but a synthesizing organ that is best set in motion by talking face to face with a fellow physician. When the powers that be at the Northland Regional Medical Program size up the physician's psyche a little better, perhaps they will make more progress in educating him.

As a start, I suggest they consider the human element. Consultation, like humor, is a human thing. It takes two to interact, and it cannot be classified, categorized, or canned. As E. B. White says in *A Subtreasury of American Humor,* Coward-McCann, 1941, "Humor can be dissected, as a frog can, but the thing dies in the process and the innards are discouraging to any but the pure scientific mind." Minnesota physicians are not yet pure scientists. And consultation, I am confident, will never be an act of pure retrieval.

Richard L. Reece, M.D.
Minneapolis, Minnesota

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*See Page 1639, October, 1969.

You May Be Right

(Continued)

As a frequent user of Dial Access Medical Library, referred to by the Editor as "canned consultation," I would like to send a few words in its defense. I find it a helpful supplement to consultants, books and journals. One advantage over some journals is that the flow of knowledge is not interrupted by crude suggestions for the use of diet pills, weird drug combinations or reference to the use of vitamin shots for the alleviation of leg cramps.

The Dial Access Library, in its own words, "is a new venture in educational communications." It was originated by the University of Wisconsin Medical School and is designed to provide twenty-four-hour availability to information in abstract form. Many of the authors give their telephone numbers if the user has further questions.

It is my understanding that not one penny of the money you grieve over was allocated to direct medical care because the private sector of medicine fought vigorously to avoid it. If the profession would not react with its usual fear and rigidity to anything federal treading on its sacred ground (but drug company money is fine), perhaps this program might be molded and developed into even greater service.

R. I. Adams, M.D
Minneapolis, Minnesota

Letter to the Editor

"I Goofed"

Bonnie, age four, and I are good friends. We seldom see one another but, when we do, we talk and "catch up" on what's happened since our previous visit.

During our last chat, Bonnie announced "I'm taking violin lessons." When I asked if she would play for me she said simply, "Yes."

She removed her small violin from the case, strung her bow, took her stance with the confidence of a seasoned performer, and began to play. I thought she was doing superbly, but suddenly she stopped and said, "I goofed." After a brief moment's hesitation, she started again and completed her "piece." No excuses, no apology, no evasion, no remorse—just a frank admission! "I goofed."

This refreshing exhibition made me wonder what the world would be like, if we who are older would emulate Bonnie's simple honesty. Suppose we acknowledged our "goofs" instead of resorting to pretense, denial, and projection. Would we feel any better—do any better? Each one of us must answer this question ourselves!

Reynold A. Jensen, M.D.
Minneapolis, Minnesota

President's Letter

The Year 1969

As the year rapidly draws to a close, we are again reminded that many of our problems are still with us, such as the doctor shortage, the lack of sufficient para-medical personnel, Medicare, Medicaid, utilization and review, as well as the high cost of medical care.

Nevertheless, this has been a good year to the extent that we are working on our Medicare and Medicaid problems, and we are in the process of developing a more workable type of utilization review that will be dealt with in a future letter.

It is a pleasure for me on behalf of the officers of the Minnesota State Medical Association, the Council, the Editors of Minnesota Medicine and the Executive Secretary and his staff to extend to all of you greetings and best wishes for a very Merry Christmas and a Happy New Year!

Delmar R. Gillespie

Delmar R. Gillespie, M.D.
President
Minnesota State Medical Association

The Editor's Soliloquy

Carcass Checkers

THERE ARE INDIVIDUALS who awaken in the morning and on arising begin to check their list of signs and symptoms, being insecure in their opinion as to whether or not they are feeling well. Though they suggest to themselves that the doctor who examined them last week found nothing wrong, they are not so sure that he was right. As they raise themselves to the sitting position at the side of their bed, they rub their brow, rotate their neck, extend their joints and feel of their back, at first in fear that they may have—, but a moment later that they may not have—, some signs and symptoms to record in their imagination. These are individuals who love their aches and pains, adroitly exaggerating and embellishing their minor maladies *ad infinitum* and cleverly contriving to inject them into their social and business conversation, as if the horrendous recital of their maladies might hopefully endow them with that extra prestige their egos seem to require. Their prodigious attachment to their chronic functional ailments is phenomenal: to abandon or disavow them would be tantamount to committing treason or heresy. What other animal than the "naked ape" is so resourceful in demonstrating and exploiting its aches and pains to the point of self-martyrdom!

"Oh, my aching bones!" "Why do I have twinges of pain in my legs?" "I cannot sleep a wink." "I lie awake and toss." "Something's got to be done, Doctor."

The aggregate of these and similar complaints constitutes a dissonant but familiar chorus to the physician's ears: a refrain reminiscent of the lamentations of Job. Job's afflictions, however, were visited upon him by an outside agency.*

Obtaining a medical history becomes an almost impossible task because of the numerous interjections of interrelated and very often irrelevant items. Facts can scarcely be distinguished from fancy when these patients insist upon proclaiming their etiology and their diagnosis.

These individuals provide lucrative support to the medical cultists who are happy to accommodate them with an affirmation of their suspicions. A three, four or six weeks course guaranteeing rehabilitation is then prescribed.

Perhaps we should be more appreciative of these individuals for it is they who make it possible for all of us to listen to the "Gee whiz" kids or the "What's your score?" or the "Win a trip" program where, between moments of this type of entertainment, we are promised guaranteed cures as substantiated by "9 out of 10 doctors"; or where one brand of acetylsalicylic acid compound is being proclaimed to be far superior to another because of its bubbling ability to reach the blood stream "fast"; or because it contains the all-powerful FX62 or some other meaningless and mysterious ingredient designed to provide instantaneous social acceptability.

"Except for my sour stomach, my aching head, my halitosis, my hyperhydrosis, my secondary anemia, my chronic insomnia, my tired bowels, my recurring borborygmus, and my irritable disposition, I'd be a well man."

Such is the character of a carcass checker.

Carl O. Rice, M.D.

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*See page 1864.

OLD DOC HESS SAYS: Don't talk about your ailments: "How are you!" is expressed with an exclamation point, not a question mark.

Distinguished Service

Harold O. Peterson, M.D.

Professor and Retiring Head
Department of Radiology
University of Minnesota

Dr. Harold O. Peterson

IN THIS issue MINNESOTA MEDICINE is featuring the specialty of roentgenology. No one could better represent in so distinguished a manner the spirit of the true Minnesota physician and the roentgenologist than Harold O. Peterson, retiring chief from the University Department of Radiology. The son of immigrant parents, born in a rural community, educated in one of Minnesota's typical small towns, Harold attained his present eminence by his own extraordinary effort and superior intelligence. In a troubled world in which the ideals, the verities once considered sacred, are being questioned or even abandoned, it is heartening to look back on the career of this unique individual and to revive once more our faith in America's institutions, her opportunities for our young people even of the most humble origins.

The Minnesota sequence of education continued when Doctor Peterson attended the University both as an undergraduate and as a medical student. It is characteristic of his tough realism that he took advantage of his need to earn his way through school by working as a laboratory technician, a splendid occupation for a potential medical student. A year in pathology in the graduate school no doubt gave him the tools needed for his critical approach to radiology. Temporarily, he deviated from this Minnesota pattern by going to the Massachusetts General Hospital for graduate work in radiology. Here he trained under the tutelage of the late Doctor George Holmes, first radiologist in the United States to establish a residency. Here too, he studied with the late Doctor Merrill Sosman, with Doctor Richard Schatzki, and many others then active in radiology in Boston. He returned to Minneapolis to become my first full time associate in the department of radiology at the University, his assignment being neuroradiology.

At its inception as a specialty, radiology encompassed all the medical uses of radiation. This pattern, however, was changing, and the division between diagnosis and therapy had already occurred in the University department. Doctor Peterson elected diagnosis, a wise choice indeed, as later events demonstrated. Roentgen diagnosis, however, was expanding rapidly and subspecialization in neuroradiology, no doubt the most difficult of all its divisions, was already in its incipiency. His intense study of this field, his meticulous attention to detail, and his manual skill all brought him rapidly to the forefront of the group concerned with the application of radiology to neurological diagnosis. He is now considered one of the foremost authorities in the field and has contributed very substantially to the development of this subspecialty.

Nevertheless he has maintained his interest and proficiency in all the ramifications of roentgen diagnosis, contributing substantially to our knowledge of gastrointestinal, urologic and chest diagnosis.

For a time, Doctor Peterson was in private practice, but continued part time at the University. His work was chiefly at the Miller Hospital in St. Paul, where he inspired an extraordinary degree of confidence in his ability, his integrity, and his leadership.

A superb teacher, with a dry and crackling wit, enormously effective because of his deceptively innocent and naive appearance, he has been in great demand as a lecturer and teacher throughout the country. His discussions and demonstrations at the annual meetings of the Academy of Neurology, sometimes running for twelve hours at a stretch, are legendary. He has been in charge of the annual teaching program of the American Roentgen Ray Society and has also carried on and greatly enlarged the traditional annual postgraduate course in radiology at the University of Minnesota. In 1957 he succeeded me as Chairman of the Department of Radiology at the University, and a more worthy choice could not have been made. Since then he has enlarged and expanded the department, which is regarded as one of the finest in America. It is notable that he was elected the first Chief of Staff at the University Hospital. It is well understood that he has had an important role in keeping the medical faculty fully aware of their responsibility to the patient. His outward, sometimes biting humor and his reserved manner actually cover a warm human being with a strong feeling of responsibility to patients—in fact, toward all mankind.

In tribute to his quality and his achievements, Doctor Peterson has received the highest honors which his colleagues in radiology could confer: President of the American Roentgen Ray Society; President of the American Board of Radiology; Chancellor of the American College of Radiology, and numerous other offices.

The whole career of this distinguished son of Minnesota has been characterized by a determined truthfulness and a complete devotion to the ideals and best practices of American medicine. Coupled with a highly critical sense of his own limitations and those of radiology is his desire for perfection which has limited his contributions. Nevertheless, Doctor Peterson has won an everlasting niche in the annals of medicine in the United States.

He is a deeply religious man, as is also his lovely and helpful wife, Margaret. Together they have brought up a fine family. Both have met good fortune and adversity with rare faith and equanimity, and together have achieved a respected and affectionate place in the hearts of their fellow Minnesotans. He will soon give up the onerous administrative duties as Chairman of his department, but will continue to contribute to Minnesota, to the United States, in fact, to the world, his knowledge, his skills and his inspired teaching. His strong spirit will still move forward, striving for further knowledge and perfection. All of his students and many friends and admiring colleagues wish him and his beloved wife many more fruitful years with happiness and contentment.

Leo G. Rigler, M.D.
Los Angeles, California

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*University of California.

Success

Someone made a survey of 1,000 successful men to learn how they got their start in life. They were not mere money-makers but were men who made the world better by their work.

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The man who says it can't be done is interrupted by the man who is doing it—Jacob Braude: Speaker's Encyclopedia

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Contraindications: Hypersensitivity to tetracyclines. *Warning:* In renal impairment, since liver toxicity is possible, lower doses are indicated; during prolonged therapy consider serum level determinations. Photodynamic reaction to sunlight may occur in hypersensitive persons. Photosensitive individuals should avoid exposure; discontinue treatment if skin discomfort occurs. *Precautions:* Nonsusceptible organisms may overgrow; treat superinfection appropriately. Tetracycline may form a stable calcium complex in bone-forming tissue and may cause dental staining during tooth development (last half of pregnancy, neonatal period, infancy, early childhood).

Side Effects: Gastrointestinal—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. *Skin*—maculopapular and erythematous rashes; exfoliative dermatitis; photosensitivity; onycholysis, nail discoloration. *Kidney*—dose-related rise in BUN. *Hypersensitivity reactions*—urticaria, angioneurotic edema, anaphylaxis. *Intracranial*—bulging fontanels in young infants. *Teeth*—yellow-brown staining; enamel hypoplasia. *Blood*—anemia, thrombocytopenic purpura, neutropenia, eosinophilia. *Liver*—cholestasis at high dosage.

Upon adverse reaction, stop medication and treat appropriately.

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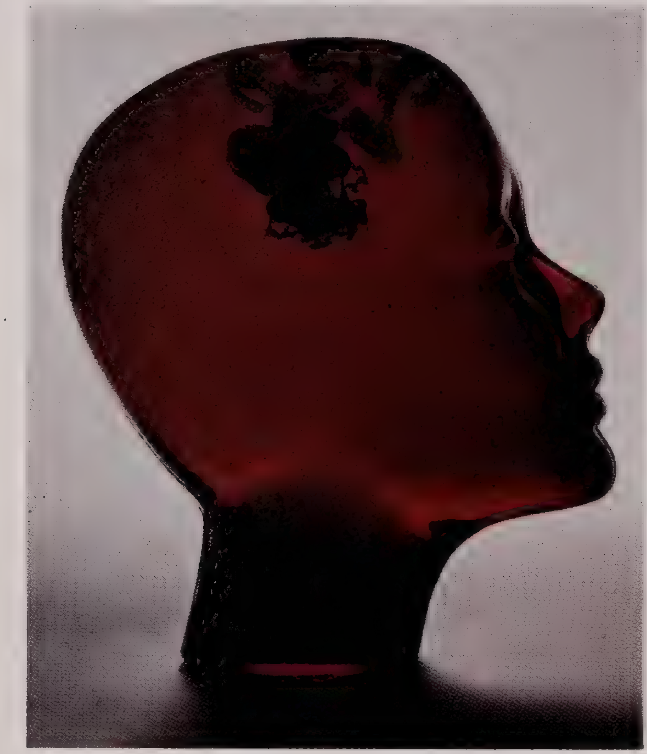
Even mild to moderate anxiety is often tinged with depression



Anxiety, even mild anxiety, seldom exists alone. Often it is mixed with depression, not necessarily of obvious and overwhelming proportions, but meaningful all the same in its effects on the patient.

In mild to moderate anxiety, consider the therapeutic edge you get with Mellaril 10 mg. t.i.d. This dosage is not only well suited to control mild to moderate anxiety, but it is also effective against the depression which might be present.

Before prescribing or administering, see Sandoz literature for full product information, including adverse reactions reported with phenothiazines. The following is a brief precautionary statement.

Contraindications: Severe central nervous system depression, comatose states from any cause, hypertensive or hypotensive heart disease of extreme degree.

Warnings: Administer cautiously to patients who have previously exhibited a hypersensitivity reaction (e.g., blood dyscrasias, jaundice) to phenothiazines. Phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides. During pregnancy, administer only when necessary.

Precautions: There have been infrequent reports of leukopenia and/or agranulocytosis and convulsive seizures. In epileptic patients, anticonvulsant medication should also be maintained. Pigmentary retinopathy may be avoided by remaining within the recommended limits of dosage. Administer cautiously to patients participating in activities requiring complete mental alertness (e.g., driving). Orthostatic hypotension is more common in females than in males. Do not use epinephrine in treating drug-induced hypotension. Daily doses in excess of 300 mg. should be used only in severe neuropsychiatric conditions.

Adverse Reactions: *Central Nervous System*—Drowsiness, especially with large doses, early in treatment; infrequently, pseudoparkinsonism and other extrapyramidal symptoms; nocturnal confusion, hyperactivity, lethargy, psychotic reactions, restlessness, and headache. *Autonomic Nervous System*—Dryness of mouth, blurred vision, constipation, nausea, vomiting, diarrhea, nasal stuffiness, and pallor. *Endocrine System*—Galactorrhea, breast engorgement, amenorrhea, inhibition of ejaculation, and peripheral edema. *Skin*—Dermatitis and skin eruptions of the urticarial type, photosensitivity. *Cardiovascular System*—Changes in the terminal portion of the electrocardiogram have been observed in some patients receiving the phenothiazine tranquilizers, including Mellaril (thioridazine). While there is no evidence at present that these changes are in any way precursors of any significant disturbance of cardiac rhythm, several sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients previously showing electrocardiographic changes. The use of periodic electrocardiograms has been proposed but would appear to be of questionable value as a predictive device. *Other*—A single case described as parotid swelling.

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for mild to moderate anxiety and anxiety with depression

The Viewing Box

Renal Mass

THE PATIENT is a 69-year-old white female who was admitted to the hospital for evaluation of vague and long-standing gastrointestinal complaints. There were no symptoms or clinical findings referable to the genitourinary system. Routine laboratory studies showed no significant abnormality; urinalysis was normal. Radiographic examination of the gastrointestinal tract disclosed diverticulosis of the colon; but no other findings were encountered. An intravenous pyelogram was performed which demonstrated a four-by-six centimeter mass density along the lower, lateral margin of the left kidney although there was no distortion of the upper collecting system. These findings were confirmed by nephrotomography. Selective renal arteriography was then performed. Representative radiographs obtained in the course of this study are reproduced below (Figures 1 and 2). The patient then underwent a left nephrectomy.

What is your diagnosis? (See next page).

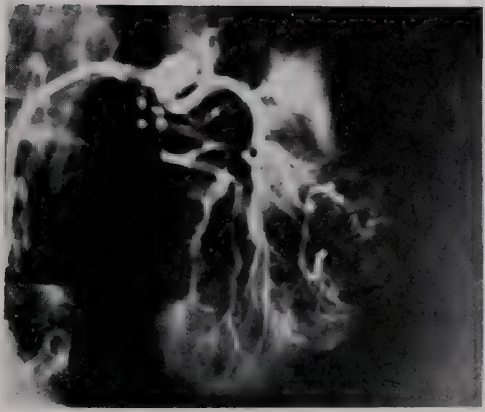

Figure 1

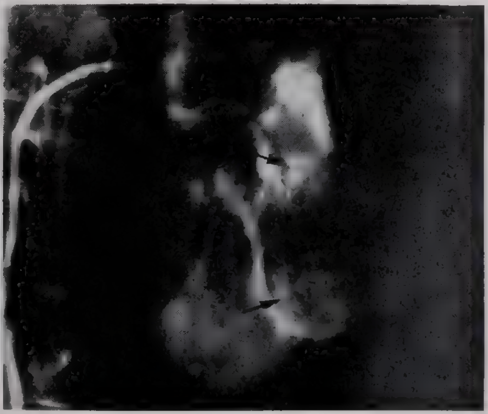

Figure 2

Diagnosis: Hypernephroma

The angiogram discloses evidence of neovascularization (arrows shown in Figure 1) and puddling of contrast medium (arrows, Figure 2) in the region of the tumor. On the basis of this examination, a diagnosis of hypernephroma was made and a nephrectomy performed. Gross pathological examination of the lesion appeared to confirm this diagnosis. Microscopic sections, however, revealed a rather mixed histologic pattern with areas of smooth muscle, lobules of adult adipose tissue and areas of an angiomatous appearance. Occasional organoid-appearing structures were encountered. The final pathologic diagnosis was angiomyolipoma of the left kidney.

In spite of the ominous appearance obtained at arteriography, the angiomyolipoma is a benign lesion classed as a hamartoma.[1] It is a relatively rare, but well-recognized, tumor which may occur in two types. In one type it is associated with tuberous sclerosis. In this instance, there are bilateral lesions which are multifocal and equally distributed between the sexes in young persons. The second type, which is exemplified in this case, is unilateral, solitary and most commonly occurs in females during the sixth or seventh decade of life. Presenting complaints are often flank pain or hematuria. Massive retroperitoneal hemorrhage may occur due to rupture of the lesion and a palpable mass may be present.[1] The patient may, as did this lady, present with nonspecific gastrointestinal complaints.[2,3]

Although renal angiography is of great value in the differentiation of benign and malignant mass lesions of the kidney, this case demonstrates that a benign lesion can, rarely, closely mimic the findings of a malignant hypernephroma.

Charles B. Lundquist, M.D.*
Minneapolis, Minnesota

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*Department of Radiology. St. Mary's Hospital.

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2. Allen, T. D. and Risk, Wm.: Renal Angiomyolipoma. J Urol 94:203, 1965.
3. Price, E. B. and Mostofi, F. K.: Symptomatic Angiomyolipoma of the Kidney. Cancer 18:761, 1965.

Early Conditioning

My first memory dates back to an incident that happened when I was four years old. I was walking with my elder sister, Sabina, pulling a little wagon in which rode the baby—my brother Philip. We were menaced by a drunkard, and we ran shrieking—my sister and I—pulling the wagon until we reached our home. Since then I have always feared drunken people, whose actions and conduct are unpredictable; and I have abominated drunkenness. Sometimes at banquets I have sat next to people who have been pouring in highballs—manhattans and triple martinis. They shout, they laugh, they emphasize their remarks by poking me and punching me—and I used to bruise easily. By such nuisances an evening has been ruined.*

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*Morris Fishbein, M.D., An Autobiography, 1969.

Dermatology

False Positive Serology

PROBLEMS CAN BE encountered in the interpretation of serologic tests for syphilis. A particularly vexing situation is the false positive reactor: a serologic state characterized by repeatedly reactive nontreponemal tests while the treponemal* tests remain nonreactive.

The occurrence of a false positive reaction is due partly to the nature of the test employed. Nontreponemal or reagin tests use cardio-lipin-lecithin as a nonspecific antigen, examples of which are the Kolmer complement fixation and Venereal Disease Research Laboratory slide flocculation tests. Reagin measured by these tests is elevated in primary syphilis four to six weeks after infection. However, reagin is not specific for syphilis but may be present in measurable amounts as a consequence of several medical conditions. Herein arises the problem of one type of false positive reactor. These reactions can be acute (less than six months' duration) or chronic (six months or longer).

Acute Reactions

Acute false positive reactions may occur following bacterial and viral infections, including vaccinations; also very high reagin titres have been recorded following infectious mononucleosis. At other times no history of prior infection or immunization is obtainable. Most often in this situation the titres are low and revert to normal within two months.

Chronic Reactions

Chronic false positive reactions are less common than the acute type. Systemic lupus erythematosus and other so-called auto-immune diseases may be associated with this condition. Yaws, pinta, and bejel frequently show positive reagin titres. This agrees with the unitarian concept that these treponematoses are merely variants of syphilis. Lepromatous leprosy, lymphogranuloma venereum, malaria, and heroin addiction have also been associated with false reactivity based upon reaginemia. Of course, the presence of these diseases does not preclude the occurrence of syphilis, a fact which can complicate diagnosis in certain situations.

There is one more type of false reaction—that of a technical nature. All normal sera may contain very small amounts of reagin. The sensitive nontreponemal tests may become even more sensitive if some of the physiochemical variables in their performance are altered. This can result in low titres being reported. About one fourth of all false positive reactions are due to such technical errors. Repeat testing discloses such a situation. Finally it should be mentioned that clerical error can occur and repeat testing is desirable before any patient is treated.

With the advent of the treponemal tests the problem of the false reaction has become somewhat less confusing. Treponemal tests are characterized by less sensitivity and greater specificity than the nontreponemal procedures. These tests use as the antigen either the protein fraction of the nonpathogenic Reiter treponeme or T. pallidum itself (viable or dead). Two of these tests are of special interest here: the Treponema Pallidum Immobilization and the Fluorescent Treponemal Antibody tests.

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*See Test Your Word Score Page 1921.

The Treponema Pallidum Immobilization test was developed first and is time-consuming as well as technically difficult and therefore costly to perform. However, until the Fluorescent Treponemal Antibody test, it was probably the chief means of differentiating the false reactor.

Differentiation

Recently the Fluorescent Treponemal Antibody test has gained favor in differentiating false positive reactions. This test uses dead T. pallidum on a microscope slide, overlaid with the patient's serum. If antibody to T. pallidum is present, this adheres and can be detected using fluorescein-labeled antihuman gamma globulin: essentially the indirect Coons' fluorescent technique. Today this test has been further refined by absorbing the serum with an extract of nonpathogenic treponemes, thus removing the treponemal "group" antibodies while specific antibodies to T. pallidum remain. This is referred to as the Fluorescent Treponemal Antibody Absorption Test.

Recent studies have demonstrated that the Fluorescent Treponemal Antibody Absorption procedure is probably the most sensitive treponemal test. Also, it is the test of choice in differentiating false positive reactors from syphilis.

In conclusion, it must be pointed out that all tests are subject to error and should not replace clinical judgment.

Willard C. Peterson, Jr., M.D.
Minneapolis, Minnesota

IT'S THE LAW

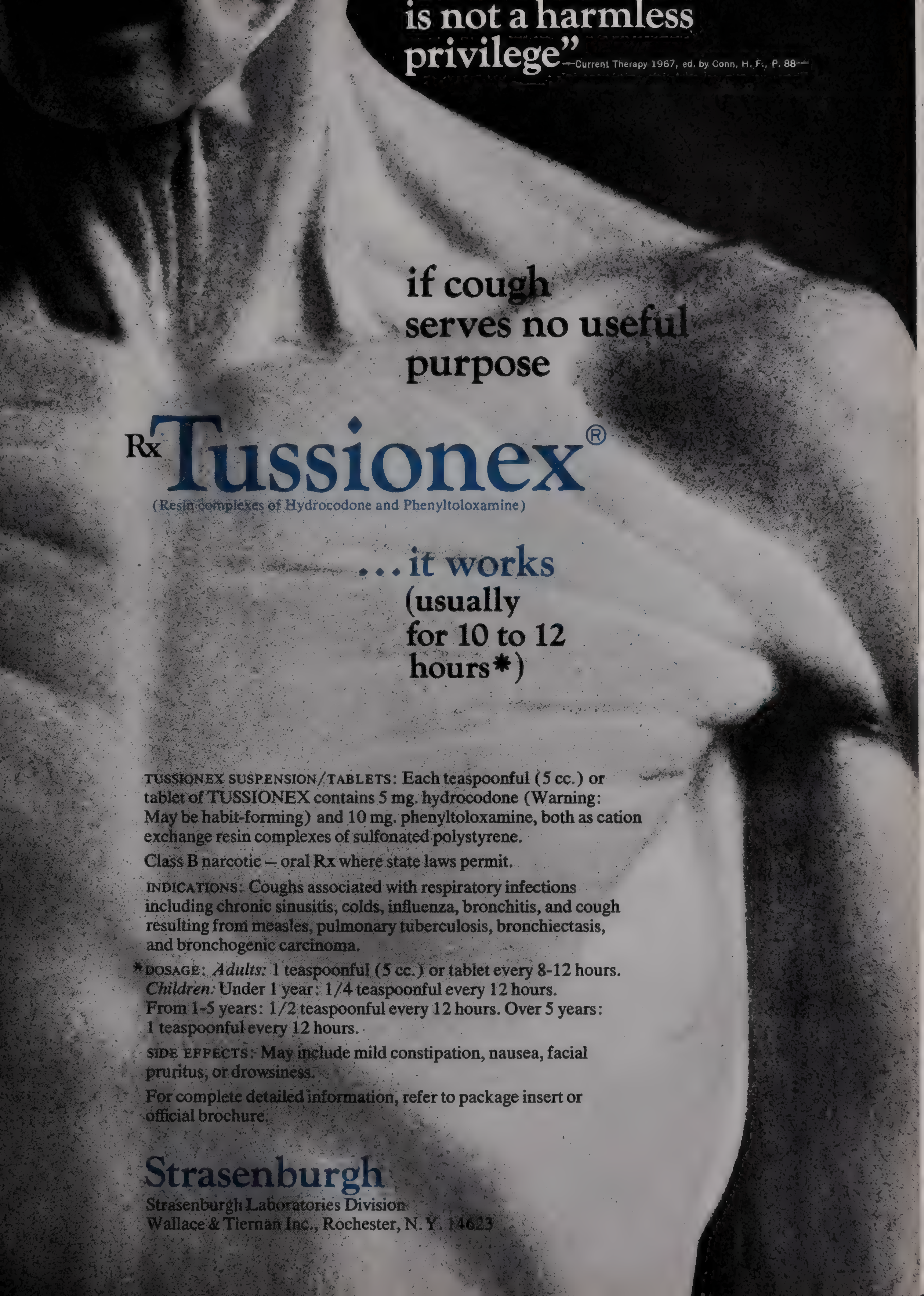
Physician's Bills Recoverable in Personal Injury Suit

A 17-year-old girl sustained severe facial injuries which required extensive plastic surgery. She was the daughter of a physician. Because of the accident, she became anxious and depressed, necessitating psychiatric treatment.

The negligent driver contended that the plastic surgeon's and the psychiatrist's bills should not be included as items of damages because the girl's father was a physician, and professional services had been rendered as a matter of professional courtesy.

The court ruled that the value of the physician's services, as well as hospital and medical bills incurred by a person injured, can be recovered even though such services are rendered gratuitously. The bills of both the psychiatrist and plastic surgeon were ordered to be paid.

Spizer v. Dixie Brewing Co., Inc., 210 So 2d 528 (La, May 15, 1968). The Citation 17:9, August 15, 1968.



is not a harmless privilege" —Current Therapy 1967, ed. by Conn, H. F., P. 88—

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*DOSAGE: *Adults:* 1 teaspoonful (5 cc.) or tablet every 8-12 hours. *Children:* Under 1 year: 1/4 teaspoonful every 12 hours. From 1-5 years: 1/2 teaspoonful every 12 hours. Over 5 years: 1 teaspoonful every 12 hours.

SIDE EFFECTS: May include mild constipation, nausea, facial pruritus, or drowsiness.

For complete detailed information, refer to package insert or official brochure.

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His heart tells him he's an invalid.
You know he's not.

Photograph professionally posed.

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Anxiety is expected in the cardiovascular patient. A little may even be desirable.

But when anxiety is exaggerated . . . when it interferes with sleep . . . when it aggravates cardiovascular symptoms, your help may be needed.

Naturally, you'll want to reassure the patient.

And perhaps prescribe Equanil (meprobamate) as adjunctive therapy. It helps relieve anxiety and tension specifically, yet gently.

Almost 15 years' use has shown that Equanil is usually well tolerated as well as effective. Side effects are generally limited to transient drowsiness; serious, therapy-interrupting side effects are rare.

Contraindications: History of sensitivity to meprobamate.

Important Precautions: Carefully supervise dose and amounts prescribed, especially for patients prone to overdose themselves. Excessive prolonged use has been reported to result in dependence or habituation in susceptible persons, as alcoholics, ex-addicts, and other severe psychoneurotics. After prolonged excessive dosage, reduce dosage gradually to avoid possibly severe withdrawal reactions. Abrupt discontinuance of excessive doses has sometimes resulted in epileptiform seizures.

Warn patients of possible reduced alcohol tolerance, with resultant slowing of reaction time and impairment of judgment and coordination.

Reduce dose if drowsiness, ataxia or visual disturbance occurs; if persistent, patients should not operate vehicles or dangerous machinery.

Side Effects include drowsiness, usually transient; if persistent and associated with ataxia, usually responds to dose reduction; occasionally concomitant CNS stimulants (amphetamine, mephentermine sulfate) are desirable. Allergic or idiosyncratic reactions are rare, but such reactions, sometimes severe, can develop in patients receiving only 1 to 4 doses who have had no previous contact with meprobamate. Previous history of allergy may or may not be related to incidence of reactions. Mild reactions are characterized by itchy urticarial or erythematous maculopapular rash, generalized or confined to groin. Acute nonthrombocytopenic purpura with cutaneous petechiae, ecchymoses, peripheral edema and fever have been reported. One fatal case of bullous dermatitis following intermittent use of meprobamate with prednisolone has been reported. If allergic reaction occurs, meprobamate should be stopped and not reinstituted. Severe reactions, observed very rarely, include angioneurotic edema, bronchial spasms, fever, fainting spells, hypotensive crises (1 fatal case), anaphylaxis, stomatitis and proctitis (1 case) and hyperthermia. Treat symptomatically as with epinephrine, antihistamine and possibly hydrocortisone. Aplastic anemia (1 fatal case), thrombocytopenic purpura, agranulocytosis and hemolytic anemia have occurred rarely, almost always in presence of known toxic agents. A few cases of leukopenia, usually transient, have been reported on continuous administration.

Meprobamate may sometimes precipitate grand mal attacks in patients susceptible to both grand and petit mal. Extremely large doses can produce rhythmic fast activity in the cortical pattern. Impairment of accommodation and visual acuity has been reported rarely. After excessive dosage for weeks or months, withdraw gradually (1 or 2 weeks) to avoid recurrence of pretreatment symptoms (insomnia, severe anxiety, anorexia). Abrupt discontinuance of excessive doses has sometimes resulted in vomiting, ataxia, tremors, muscle twitching and epileptiform seizures. Prescribe very cautiously and in small amounts for patients with suicidal tendencies. Suicidal attempts have resulted in coma, shock, vasomotor and respiratory collapse and anuria. Excessive doses have resulted in prompt sleep; reduction of blood pressure, pulse and respiratory rates to basal levels; and occasionally hyperventilation. Treat with immediate gastric lavage and appropriate symptomatic therapy. (CNS stimulants and pressor amines as indicated.) Doses above 2400 mg./day are not recommended.

Composition: Tablets, 200 mg. and 400 mg. meprobamate. Coated Tablets, WYSEALS® EQUANIL (meprobamate) 400 mg. (All tablets also available in REDIPAK® [strip pack], Wyeth.) Continuous-Release Capsules, EQUANIL L-A (meprobamate) 400 mg.

Wyeth Laboratories Philadelphia, Pa.

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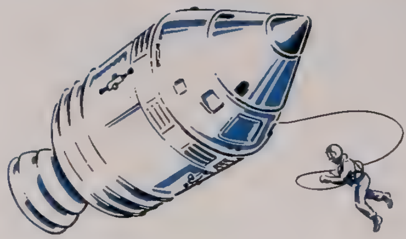

Man in space, now fait accompli, re-emphasizes the importance of Uro-Phosphate therapy. Research into the effect of space travel on the astronaut reveals that weightlessness causes loss of bone calcium. As the bones are required to bear less and less of the weight of the body they lose calcium, increasing the calcium content of the urine. When physical activity is reduced, the acidity of the urine should be adjusted to keep increased calcium in solution . . . . a prophylaxis to prevent kidney or bladder calculi.

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Carcinoma of the Prostate

The Rationale of Therapy

As for any neoplasm, the rationale of therapy in carcinoma of the prostate depends on the evaluation of three basic factors: (1) the risk of the untreated tumor, (2) the potential risks and benefits of the proposed therapy, and (3) the comparative potential risks and benefits of the therapeutic alternatives. The evaluation of these three basic factors depends on a knowledge of the pathology and natural history of prostatic carcinoma and of the results achieved by each therapeutic modality. Recent advances in these areas have created a state of flux.

Recent Advances

The Role of the Lymphatics

One of the most important advancements in the basic pathology of prostatic carcinoma is the recognition of the role of the lymphatic vessels in the dissemination of the disease. Lymphangiography has shown a distribution of lymphatic vessels pursuing a course similar to that of the vertebral plexus of veins and, importantly, has shown direct communications between the lymphatic vessels and the veins of the pelvis.[1]

The Lymph Nodes

Regional metastasis of cancer of the prostate is most often to the external iliac, hypogastric, and sacral nodes.[2] From these regional nodes the cancer may metastasize to the periaortic nodes and occasionally to the cervical and supraclavicular nodes. The inguinal nodes are rarely involved.

It has been emphasized that advanced prostatic cancer (by clinical appraisal) need not be present for nodes to be metastatically involved. Arduino and Glucksman[3] reported 71 patients in whom clinical appraisal revealed cancer limited to the prostate and who underwent radical prostatectomy. About 27% had metastatically involved pelvic lymph nodes. Microscopic evidence of involvement of the prostatic capsule without actual perforation was not associated with an increased incidence of nodal metastasis (7% nodal metastasis). However, microscopic invasion of the seminal vesicles was associated with an 82% incidence of pelvic nodal metastasis. These authors believed that, when local extension of the tumor beyond the prostate is evident clinically, the incidence of pelvic lymph node metastasis approaches 100%.

Hematogenous Dissemination

It has been postulated that cancer cells are diverted by lymph node metastasis from their usual lymphatic channels and are carried through the alternate lymphatic vessels, investing the bony pelvis and vertebrae, together with the vertebral plexus of veins.[1] It is important to recall that there is free communication between the pelvic veins and the vertebral plexus of veins,[4,5] and that early hematogenous dissemination is possible in this disease.

Perineural Involvement

Perineural involvement with carcinoma, formerly believed to be in perineural lymphatic vessels, is now known to be in perineural spaces. This finding is pathognomonic of carcinoma and is helpful in differentiating low-grade carcinoma from adenoma, but occurs in 80 to 90% of all carcinomas and is prognostically meaningless.[6,7]

For many years it has been recognized that prostatic cancer is usually multicentric in origin and may begin in any one or several of the five lobes of the prostate. This belief is opposed to the earlier one in which the cancers arose from a single focus almost always in the posterior lobe. The carcinomas are also known to arise in most cases in the periphery of the prostate in a subcapsular position far removed from the prostatic urethra. Obstructive symptoms are, therefore, unusual in the early phase.

Cellular Differentiation and Clinical Staging

Another important investigation in the basic pathology of prostatic carcinoma has been an attempt to relate prognosis with systems of classification that incorporate a combination of cell differentiation and histologic pattern with and without clinical staging.[8-10] Utz and Farrow[11] found that the histologic grade of prostatic cancer is the most valuable guide to the growth rate of the tumor and survival of the patient, but that clinical staging of the cancer based on symptomatic manifestations, digital rectal evaluation of extension, and laboratory or roentgenographic evidence of distant metastasis must be considered in the total profile of this diverse tumor. Although these authors believe that the combined clinicopathologic evaluation will greatly improve the accuracy of prognostication, they expect forthcoming help from current research in prostatic enzymology and histochemistry.

Clinical Staging

Proper staging of prostatic carcinoma is as important as cellular differentiation in the selection of treatment and enables comparisons of different forms of therapy. The World Health Organization clinical staging system divides all prostatic cancers into four stages based on the results of rectal examination, roentgenographic studies of the skeleton, prostatic or total serum acid phosphatase determinations, and biopsy from the prostate (Table 1).

At the Mayo Clinic, the staging system incorporates more tests of metastatic involvement (Table 2), but in this discussion the staging system of the World Health Organization will be used because most of the literature currently available employs that system.

Natural History of Untreated Prostatic Carcinoma

Stage I—"Untreated"

Comparisons between the incidence of stage I carcinoma of the prostate found incidentally at autopsy or surgery and the mortality rate of patients with stage III or IV prostatic cancer reveal a large discrepancy. The natural history of most stage I carcinomas of the prostate is sufficiently long to allow the patient to die of other causes.[13]

In stage I or occult cancer of the prostate, the operative procedure that led to the discovery of the cancer may alter the natural course of the disease. Greene and Simon[14] reported six cases in which the diagnosis of occult carcinoma was made on the basis of transurethral resection specimens but in which subsequent specimens taken during transurethral resection or suprapubic prostatectomy failed to show carcinoma. Likewise, in 14 patients in whom occult carcinoma was found, subsequent radical prostatectomy failed to reveal cancer in five.[15] These and other reports confirm that occult carcinoma occasionally can be eliminated by conservative prostatectomy (simple perineal, suprapubic, retropubic, or transurethral). Thus there is no such patient as one with "truly untreated" stage I prostatic cancer. Nevertheless, this is the type of patient that can be considered in this group.

The study by Bauer and associates[16] has shown that the survival rates in microscopically well-differentiated lesions was 75% at five years and 47% at 10 years. Poorly differentiated lesions are associated with survival rates of 33% (24 patients) and 14% (seven patients) at five and 10 years respectively.

Greene and Simon,[14] using material from transurethral resection specimens, found overall survival rates of 70.7 and 39.4% at five and 10 years, respectively. These survival rates are 95 and 85% of the normal actuarial survival rates for patients of the same age without cancer. Most studies confirm these figures.

Melicow[17] believes that latent prostatic carcinoma in the elderly patient tends to have a low lethal potentiality, whereas in the younger patient this type of cancer is highly invasive locally and early metastatic spread is likely. Bailar and associates,[18] however, believe that a prostatic carcinoma of any given histologic grade is no more malignant in a young person than in an elderly patient.

The bulk of the present information indicates that prognosis in stage I prostatic cancer is dependent to some extent on the histologic grade of the lesion but that most men with stage I carcinoma will die with their disease rather than of it.

Stage II—"Untreated"

Andersen[19] reported two five-year and one 10-year survivor among 11 patients who had received no treatment. Cook[20] reported a 10-year survival rate of 24% in 25 cases.

The natural history of some stage II lesions must be long, as evidenced by local recurrence or metastasis after apparent cancer-free periods of five, 10, or even 15 years. However, it is obvious from the survival rates of patients with stage II cancer who have been treated that it is a potentially lethal tumor with an approximate mortality rate of not less than 50% in five years if left untreated.[13]

In the paper by Shelley and associates[8] previously mentioned, most patients who were suitable for radical prostatectomy (those with stage I or II lesions clinically) had histologically higher grade tumors. In Culp's[21] series of 123 patients selected for radical prostatectomy, 113 had histologic grade I or II lesions. The poor prognosis of the unusual (four of 92 cases) undifferentiated carcinoma in a clinically stage II lesion, even with treatment, was also borne out in the recent series by Jewett and associates.[22] All four of his patients died.

From our present knowledge, the indication is that the natural history of stage II carcinoma of the prostate varies with the histologic differentiation of the cancer. It should be emphasized, however, that among the histologically well differentiated lesions, differences in grading are not a good basis for prognostica-

TABLE 1

World Health Organization Staging System for Pathologic Proof of Prostatic Cancer

Stage	Rectal examination	Acid phosphatase	Bone survey	Percentage of all patients presenting with prostatic cancer[12]
I	Findings negative	Normal	Negative	5
II	Localized nodule	Normal	Negative	8
III	Extraprostatic extension	Normal	Negative	48
IV	Findings may vary	Elevated or	Positive	39

TABLE 2

Mayo Clinic Staging System for Pathologic Proof of Prostatic Cancer

Stage	Rectal examination	Acid phosphatase	Bone survey	Bone scan	Bone marrow
0	Findings negative	Normal tartrate inhibited fraction; total may be slightly elevated	Negative	Negative	Negative
I	Localized nodule (<1.5-cm diameter)	Same as above	Negative	Negative	Negative
II	Localized nodule (>1.5-cm diameter)	Same as above	Negative	Negative	Negative
III	Extraprostatic extension	May be elevated	Negative	Negative	Negative
IV	Findings may vary	Elevated (with one of the following positive)	Positive	Positive	Positive

tion in an individual case. In this group, the latent and the lethal lesions look alike.

Stage III—"Untreated"

Untreated stage III carcinoma of the prostate appears to have a more uniformly lethal potential. A number of large series have noted that survival rates ranged from 5 to 15% for five years and averaged about 5% for 10 years. However, many of these series overlap into the "preacid-phosphatase era", and undisclosed numbers of the patients had no bone surveys, so that many of these patients would now have been grouped with patients who had stage IV lesions. Thus these figures may be low.

A recent study by the Veterans Administration research group,[12] of 2,057 prostatic cancer patients, including 983 with stage III lesions, revealed a startlingly high five-year survival rate of 57% for untreated patients.

Preliminary reports[8] indicate a relatively high incidence of histologically undifferentiated carcinomas in stages III and IV and a rather low incidence of differentiated or grade I tumors. However, there is no completed study of the variation of survival with histologic grade in stage III untreated carcinomas of the prostate.

Stage IV—"Untreated"

Stage IV or metastatic carcinoma of the prostate is associated with a grim prognosis. Patients with untreated stage IV disease have a five-year survival rate of between 0 and 20%.[12] The average survival of untreated patients with stage IV disease is about one year.

The Risks of Therapy

The two more commonly used treatment modalities are surgery and antiandrogenic therapy.

Surgery

According to Whitmore[13] the following ablative procedures might be logically considered in the surgical attempt to eradicate prostatic cancer: (1) radical prostatectomy (either perineal or retropubic approach), (2) radical prostatectomy with regional lymph node dissection, (3) prostatectomy and simple total cystectomy, (4) prostatectomy and radical cystectomy, and (5) pelvic exenteration.

The operative mortality rates from these ablative surgical procedures range from 1 to 5% with radical prostatectomy, through 10 to 15% for simple or radical cystectomy, to about 20% with pelvic exenteration.

All these procedures will almost invariably lead to loss of sexual function. Radical prostatectomy carries a risk of urinary incontinence. Cystectomy necessitates the hazards and inconveniences of urinary diversion and, in the case of pelvic exenteration, a colostomy as well.[13]

Antiandrogenic

Since 1941, when Herbst[23] and Huggins and Hodges[24] reported the first of many experiences with the antiandrogenic therapy of prostatic cancer, various estrogens have been used. Most are synthetic. Diethylstilbestrol is the most commonly used.

Although it is the best drug therapy for prostatic cancer, estrogen therapy is not innocuous, contrary to prevailing opinion. It causes embarrassing and often painful gynecomastia, changes in the skin and fat distribution, testicular atrophy, and decrease in or loss of libido. It may also interfere with obtaining a positive tissue diagnosis by biopsy in the future.

An even more important controversy is that some estrogens may decrease the patient's life expectancy, primarily by increasing the incidence of cardiovascular complications.[12] Significantly, a recent study by Hanash and coworkers[25] has shown that there was not an increase in coronary artery or aortic atherosclerosis in estrogen-treated prostatic cancer patients, but that estrogens did increase the risk of congestive heart failure.

Orchiectomy, which has a low associated operative morbidity and a low mortality rate, has perhaps its greatest risk in the psychologic effects it causes.

The Results of Therapy

Stage I—Subtotal Prostatectomy

Bauer and associates[16] have shown a decreased survival rate in the unusual patients with stage I prostatic cancer that is histologically poorly differentiated. More often the patient with low-grade stage I cancer has a favorable prognosis (Table 3).

Greene and Simon[14] noted a five-year survival rate of about 71% for their patients who had transurethral resection only. Montgomery and associates[27] studied 35 patients who had had stage I carcinoma for at least eight years. At the time of their report no patient had died of prostatic cancer. Labess[26] traced 33 patients who had had stage I carcinoma treated by suprapubic enucleation and found that 85% lived five years or more.

Subtotal prostatectomy plus antiandrogenic therapy in stage I cancer do not reveal a favorable effect on survival. In Greene and Simon's[14] series the five-year survival of patients treated by transurethral resection plus diethylstilbestrol was 67%, as opposed to about 71% for patients treated by transurethral resection alone.

TABLE 3

Survival After Therapy for Stage I Prostatic Cancer

	Survival, %		
Author	5 yr.	10 yr.	Treatment
Bauer and associates[16]	75	47	Suprapubic prostatectomy (conservative)
Greene and Simon[14]	70.7		Transurethral resection
		39.4	Transurethral resection
	67		Transurethral resection and estrogens
Labess[26]	85		Suprapubic enucleation
Bauer and associates[16]	33*	14*	Suprapubic prostatectomy (conservative)
VA study group†[12]	85		Radical prostatectomy and placebo
	75		Radical prostatectomy and estrogen

*Lesions were poorly differentiated.

†Stages I and II combined.

TABLE 4

Survival After Therapy for Stage II Prostatic Cancer

	Survival, %			
Author	5 yr.	10 yr.	15 yr.	Treatment
Andersen[19]	18	9		None
Cook[20]		24		None
Jewett and associates[22]	75*	47*	35	Radical perineal prostatectomy
Jewett[28]	61	37		Radical perineal prostatectomy
Turner and Belt[29]	51	34		Radical perineal prostatectomy
Leadbetter and associates[30]	70+ 50†	40 12†		Radical prostatectomy
Culp[21]		71‡		Radical prostatectomy
Barnes[31]	53		33	Estrogen
Andersen[19]	65	35		Estrogen

*Figures are taken from survival curves and are approximate.

†Poorly differentiated lesions.

‡Nodule less than 1.5 cm.

In the series of patients with occult carcinomas reported by Bauer and co-workers,[16] no demonstrable increases were seen in the survival rates for patients who received estrogens or who underwent castration. This observation applied to patients with well-differentiated lesions as well as to those with poorly differentiated lesions.

Stage I—Radical Prostatectomy

The most recently published large series of patients with stage I carcinomas treated by radical prostatectomy is that of the 161 patients in the Veterans Administration group study.[12] Of these, only one patient died of prostatic cancer during the five-year period reported.

Stage II (Table 4)—Radical Prostatectomy

The prognosis is affected by the histologic grade of the lesion. Because the staging system is a clinical one, the percentage of patients with disease limited to the prostate (as proved by examination of the surgical specimen) in any given series will greatly affect the survival statistics of that series.

Survival curves reported by Jewett and associates[22] over a 15-year period (Table 5) were in close agreement with those of Turner and Belt,[29] who reported a 43% 10-year survival rate after radical perineal prostatectomy.

Leadbetter and associates[30] also confirmed the influence of histologic grade on survival after radical prostatectomy by their report of overall five- and 10-year survival rates of more than 70% and of 40% as compared to 50% and 12% for patients with poorly differentiated tumors.

In a series of patients with localized nodules less than 1.5 cm in diameter, Culp[21] noted a 10-year survival rate of 71%. In larger lesions confined to the prostate, the 10-year survival was 54%. In his series Culp found that patients with grade I lesions had a 50% better chance of 10-year survival than did those with comparable grade II cancers.

Stage II—Antiandrogenic Therapy

Jewett[32] in 1963 reported an extended study of 40 patients with stage II cancer who were followed for 15 years or more after radical perineal prostatectomy. All had microscopic confirmation of cancer limited to the prostate; the survival rate at 15 years was 30%.

In *22* comparable patients with stage II lesions (but without microscopic confirmation of limitation to the prostate) treated by Barnes[33] with endocrine therapy alone, the survival rate was 32% at 15 years.

Andersen[19] reported five and 10-year survival rates of patients with stage II cancer treated with endocrine therapy as 65 and 35%, respectively.

The recent Veterans Administration study group series,[12] although of limited comparative value because of only a five-year follow-up and because they have considered stage I and stage II cancers together in their reporting, may be useful for comparison of survival rates of radical prostatectomy alone versus radical prostatectomy plus estrogen therapy. According to that report the detrimental effect of estrogens on the survival rate was considered statistically significant and produced a 10% decrease in survival rate (from 85 to 75% five-year survival). However, many authorities believe that if a high-grade lesion is found at operation or if extension beyond the prostatic capsule is discovered on review of the microscopic section or if both are noted, antiandrogenic therapy should be initiated immediately.

Stage III—Radical Prostatectomy

Radical prostatectomy is rarely done in the presence of clinical extension beyond the prostate because of its limited value. However, a number of investigators have studied the results in patients who were believed to have stage II cancers, who underwent prostatectomy, and who were found to have extension beyond the capsule of the prostate. Jewett[28] reported a 10-year survival rate of 23% for such patients and 12.5% for those with clinical stage III disease. Turner and Belt[29] reported five- and 10-year survival rates of 47 and 25%, respectively, for patients with stage III cancer treated by radical prostatectomy; but they may have had several patients with stage II lesions in their series.

Whitmore and Mackenzie[34] reported that none of the 17 patients with stage III cancer who were treated by either radical cystectomy or pelvic exenteration were cured.

Stage III—Antiandrogenic Therapy

The experience with antiandrogenic therapy in stage III prostatic carcinomas is summarized in Table 6. According to Emmett and co-workers,[10] orchiectomy achieved the best results when done before metastasis appeared and diethylstilbestrol did not seem to improve survival statistics.

Although all these reported survival rates are about the same, the recent study by the Veterans Administration group has raised some issues about the estrogen treatment of prostatic cancer. Figures in that study indicate that although estrogen-treated patients have a decreased mortality rate from prostatic cancer the mortality rate from cardiovascular complications is increased.

In stage III lesions, a combination of endocrine therapy followed by surgery was employed by Scott.[39] In a series of 31 patients selected because of their responsiveness to endocrine therapy, a 10-year survival rate of 61% after radical perineal prostatectomy was observed.

TABLE 5

Fifteen-Year Survival Rates in Prostatic Cancer

Criterion	Survival, %
Grade of histologic differentiation	
Grade 1	28
Grade 2	32
Grade 3	0
Extent of local spread*	
Confirmed intracapsular	40.7
Confirmed extracapsular	5.9

*As determined by microscopic examination of surgical specimen. Overall survival rate according to extent of spread was 35%. (Modified from Jewett, H. J., Bridge, R. W., Gray, G. F., Jr., and Shelley, W. M.: The Palpable Nodule of Prostatic Cancer: Results 15 Years After Radical Excision. JAMA 203: 403, 1968.)

TABLE 6

Survival After Therapy for Stage III Prostatic Cancer

	Survival, %		
Author	5 yr.	10 yr.	Treatment
Andersen[19]	5.2		None
Emmett, Greene, and Papantoniou[10]		5.1	None
Ganem[35,36]	26.6		Estrogen
	46.1	15.2	Orchiectomy and estrogen
Nesbit and Baum[37,38]	29.0		Estrogen
	31.2		Orchiectomy
	43.6		Orchiectomy and estrogen
Emmett, Greene, and Papantoniou[10]	15.4		None
	35.4		Estrogen
	58.6		Orchiectomy
	55.8		Orchiectomy and estrogen
		11.5	Estrogen
		27.3	Orchiectomy
		25.9	Orchiectomy and estrogen
Andersen[19]	32.8	4.0	Estrogen
Turner and Belt[29]	47	25	Radical prostatectomy
Jewett[28,32]		12.5	Radical prostatectomy

Stage IV—Antiandrogenic Therapy

No direct surgical therapy is possible for clinically metastatic or stage IV cancer of the prostate. The most often used therapy is antiandrogenic. Orchiectomy is the best palliative therapy. When the cancer becomes resistant to one type of estrogen, alternation of estrogen preparations may induce a symptomatic remission. Diethylstilbestrol diphosphate has been shown to be potentially useful.[40]

Additional forms of hormonal manipulation include (1) the exogenous administration of corticosteroids, (2) bilateral adrenalectomy, (3) ablation of the pituitary gland either surgically or by irradiation, and (4) progestational agents.[41]

Stage IV—Radiation Therapy

External-beam irradiation of painful skeletal metastasis has provided a significant palliative effect in a large percentage of patients. The tumor dose delivered to a particular metastatic site in bone usually varies from 1,200 to 2,500 rads.

An additional method of relieving bone pain from prostatic cancer metastasis is systemic irradiation with radioactive phosphorus, ^{32}P, a beta-emitter with a half-life of 14.3 days. The uptake of ^{32}P in the osteoblastic metastasis is said to be increased 15 to 20 times by the administration of male hormones.[42] Thus ^{32}P is usually given during a course of testosterone. Recently Kaplan and associates[43] have noted favorable results in metastatic prostate cancer, using polymetaphosphate labeled with ^{32}P.

Radiotherapy for Cure

Historically, radiation therapy has been considered important in the palliative treatment of prostatic cancer. However, the challenging role of radiotherapy is that of primary treatment with curative intent.

In the past there have been varied attempts to cure prostatic carcinoma by employing ionizing radiation. The interstitial irradiation techniques with radon seeds or radium needles often failed, presumably because of their inability to achieve homogeneous dosage distribution within the tumor. An additional factor of concern was the tissue toxicity of the high dose, since the radiation was delivered in a necessarily short time.

Orthovoltage Irradiation

The scope of orthovoltage irradiation as an adjunct to interstitial therapy was limited. External irradiation with orthovoltage equipment produced severe skin reactions involving the perineum, genitalia, and anus when efforts were made to deliver a significant dose to the prostate.

In 1951 Flocks[44] introduced the technique of interstitial injection of radioactive gold into the prostate and seminal vesicles. Various anatomic approaches were used. In selected patients treated by Flocks and a few others experienced in this technique, favorable results were accomplished. These results have proved to the satisfaction of many the ability of radiation to destroy adenocarcinoma of the prostate. The procedure has the same disadvantages that other forms of interstitial irradiation have, that is, the inability to achieve a sustained and evenly distributed irradiation of the tumor.[45]

Supervoltage Radiotherapy

Within the past few years, supervoltage radiotherapy has been employed with curative intent in patients with prostatic carcinoma confined to the pelvis; but to date there are only a few reports in the literature on this subject. In 1965 Bagshaw, Kaplan, and Sagerman[46] reported the use of x-rays produced with a 4.7-Mev linear accelerator in the treatment of 81 patients with prostatic carcinoma. Also in 1965, George and associates[47] reported using cobalt-60 teletherapy to treat nine patients. Del Regato[45] in 1967 reported using cobalt-60 teletherapy in seven patients with prostatic cancer, and in 1968 Bennett[48] reported cobalt-60 teletherapy in 11 patients.

Patient Selection

The method of patient selection*, although not specifically stated in several of these preliminary reports, seems to follow that of Bagshaw and associates:[46] (1) the patient must have carcinoma proved by biopsy, (2) the carcinoma should be localized to the region of the prostate, its capsule, or the immediate periprostatic tissue, with no hematogenous metastasis, and (3) either the cancer must be too extensive for radical prostatectomy or the patient must have refused surgery.

Interestingly, both Bagshaw and George advocate treatment in the presence of an elevated level of acid phosphatase if the bone survey is negative. Most of the recent literature has stated that if the level of acid phosphatase is elevated, the patient is considered to have stage IV or metastatic cancer. Recent knowledge of the frequency of lymph node involvement in clinical stage III disease makes it difficult to meet the second criterion of patient selection, previously listed. Perhaps lymphangiography will help in this regard.

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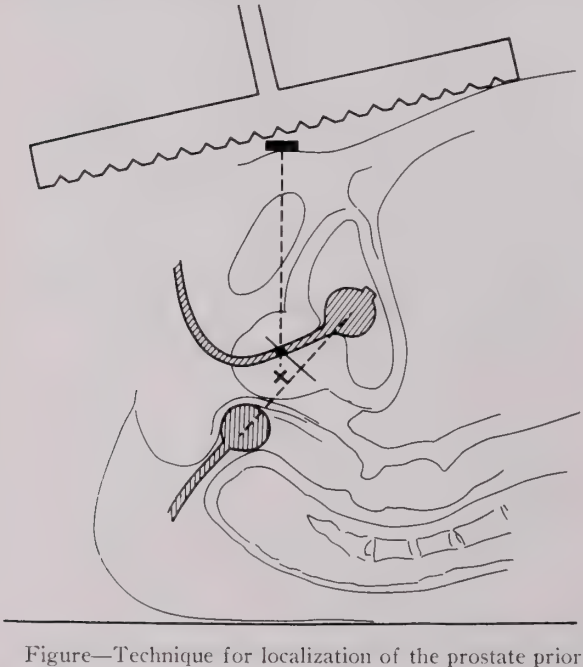
*Schirmer and Scott[49] believed that the rationale for irradiation in prostatic cancer should be based on differentiation and catalase activity of the cancer cells. They postulated that irradiation destroys prostatic cancer because of a combination of hydrogen peroxide formation and decreasing catalase activity, the latter found with increasing dedifferentiation of prostatic cancer cells.

Treatment Planning and Delivery Techniques

Treatment planning techniques vary among reporting institutions. Like those in other institutions who use either rotational or cross-firing methods, our group at the Mayo Clinic employs confirmatory localization films of the treatment area. The current method (Figure) consists of placing a mark with ink on the patient's skin over the center of the symphysis pubis in the midline. The patient then goes to the urology subsection of the diagnostic radiology department where a lead marker is placed over the ink mark and taped in place, a Foley catheter is inserted into the urinary bladder, and the balloon, filled with contrast medium (69% Renovist), is pulled down firmly against the prostate. Next, a catheter is inserted into the rectum, the balloon is filled with Renovist, and an across-the-table lateral roentgenogram is taken, with the central axis being at the level of the lead marker and with a distortion scale placed in the midline. The superior and posterior surfaces of the prostate gland are delineated by the contrast medium in the catheter balloon and rectum, respectively, while the urethra is demonstrated by the medium in the lumen of the catheter. The center of the prostate gland is judged to be 1 cm posterior to the prostatic urethra.

The roentgenographically localized center of the prostate gland is then related to the skin marker, and the distance from the skin to the center of the prostate is measured, with correction being made for magnification (as indicated by the distortion scale).

Although several different techniques have been employed in the past five years in delivering high-dose external radiation therapy to the prostate, the technique most commonly used at the Mayo Clinic employs the 6.3-Mev linear accelerator and multiple cross-firing beams intersecting the predetermined center of the prostate. Either three or five cross-firing portals are generally used, depending on the choice of the therapist and the calculated dose-distribution pattern for the individual patient. If three portals are used, one is anterior and two are posterior; if five portals are used, three are anterior and two are posterior. The midline is avoided on all posterior portals.



Figure—Technique for localization of the prostate prior to rotational or cross firing beam radiotherapy.

The portal size is a maximum of 8 by 8 cm at the center of rotation. According to the preference of the therapist, treatment may be directed through each of several portals daily. The common daily tumor dose is 180 rads to the 100% isodose contour. The total tumor dose is 6,000 to 6,500 rads to the 100% isodose contour is six to seven weeks of treatment. Split-course therapy is employed.

Details of the techniques used by the other reporting centers in delivering high-dosage irradiation to the prostate may be obtained by review of their published reports.[45-48]

Sequelae

A high percentage of patients undergoing high-dose irradiation to the prostate will have mild-to-moderate dysuria and diarrhea. These symptoms usually begin about 10 days after the initiation of therapy and, if no symptomatic treatment is given, persist for several weeks after the completion of therapy. In nearly all patients the symptoms are easily controlled. To date we have encountered no serious complications, such as rectal or bladder hemorrhage or rectal ulcer requiring surgical intervention. An occasional patient has required dilatation of the urethra after therapy. In general the symptoms are transient, mild, and easily controlled.

With many of the patients treated by radiation therapy, data on potency have not been collected before and after treatment. In Bagshaw and associates'[46] series of 18 patients on whom information was available 14 reported no change in potency whereas four noticed decreased potency. Two of George and associates'[47] patients were reportedly potent after treatment; information was not given on the remainder. Certainly the data pertaining to potency after treatment are important and should be gathered in future reports.

Efficacy of Treatment

All the investigators who have reported the use of supervoltage radiotherapy of prostatic carcinoma seem highly encouraged, and many centers are enthusiastic and frankly optimistic. Unfortunately, none of the series reported to date have been controlled series. Few of the patients have been traced for even five years; yet in prostatic cancer studies 10-year survival rates are required to provide a reliable guide for the efficacy of treatment. Furthermore, many of the patients have had prior surgical therapy or previous or continuing hormonal therapy. Some have even had previous instillations of ^{198}Au. At the present time it is impossible to give any meaningful survival figures or comparisons of one method of therapy (radiation versus surgery with or without hormones) with another.

Bagshaw and co-workers[46] summarized their experience by stating that 64 of 73 patients had striking alleviation of local symptoms and that 13 of 30 survived at least five years without evidence of local recurrence or distant metastasis. The five-year survival rate of the entire group, as computed by the actuarial method, was 54%.

As a result of their experience, Bagshaw and associates believe that survival rates after radiotherapy are comparable to rates after radical surgery and that there is less hazard to the patient and less disturbance of normal function. Del Regato[45] optimistically believes that certain types of radiotherapy will rapidly become the treatment of choice for all prostatic carcinomas (operable or inoperable) confined to the pelvis.

Work in Progress

A protocol study of carcinoma of the prostate has been undertaken at the Mayo Clinic in which there are five specific aims: (1) to determine the growth-rate pattern of prostatic carcinoma as related to age at onset, histologic grade, and clinical stage; (2) to determine the growth-rate pattern response to endocrine therapy, radical prostatectomy, and radiation therapy, as compared to untreated controls; (3) to determine the risks of the three treatment methods, as compared to the risk of the untreated cancer; (4) to determine the growth-rate pattern response to combinations of the three treatment methods, as compared to utilization of a single treatment method; and (5) to establish a reasonable clinical approach to the management of the patient who has not received conventional surgical, radiologic, or hormonal therapy.

In addition, because of the recent studies indicating the possibility of lymphogenous metastasis in clinical stages II and III prostatic carcinoma (probably about 25% and more than 90%, respectively), a study is planned incorporating lymphangiography before therapy (either surgery or irradiation or both). Lymphangiography should be a useful tool in assessing the extent of macroscopic disease and, consequently, an aid in determining the type and extent of the therapy employed.

Concluding Comments

The rationale of therapy is changing owing to recent advances in our knowledge of the pathophysiology of prostatic cancer. It has been shown that prostatic cancer is often multicentric in origin, may arise in any of the five lobes of the prostate, is usually subcapsular in origin, and involves lymphatic vessels more frequently and earlier than previously thought.

Staging and Grading

Knowledge of the natural history of untreated prostatic cancer is still incomplete but appears to follow a certain pattern. Occult or stage I cancer is almost always low grade and pursues an indolent course whether or not treatment is given. Stage II cancer (the localized nodule) is also usually low grade, but its natural history varies within the clinical stage, depending to some degree on histologic grade and microscopic extent of the tumor. Among the lower grade stage II cancers, some are lethal and others are indolent; there seems to be no way at present to distinguish between these. Little is known of the natural history of untreated stage II prostatic cancer. Stage III (local extension beyond the capsule) cancer is usually microscopically a high-grade maligancy, and less variation of its natural history is evident within the clinical stage. Untreated, it is more uniformly lethal. Stage IV represents metastatic prostatic cancer (usually high grade) and if untreated is uniformly lethal. Because of variations in the natural history, especially of stage II lesions, follow-up data on large groups of patients in well controlled series over long (10 to 15 years) periods are needed to elucidate the natural history of the lesions.

All the present forms of therapy for prostatic cancer have both risks and benefits. From the literature reviewed, the following conclusions may be drawn.

Stage I

In stage I, the so-called occult carcinoma of the usual low grade, the risks of radical surgery, hormone therapy, or high-dose radiation therapy probably outweigh the potential benefits to the patient. These patients do well with no further treatment and with regular follow-up. In the rare high-grade stage I carcinoma diffusely distributed throughout the prostate, treatment (either surgery or high-dose radiotherapy) appears indicated.

Stage II

In stage II cancer, treatment is indicated. Surgery will give good results if the lesion is low grade and microscopically confined to the prostate. Therefore the percentage of patients with stage I or II prostatic cancer considered operable is of utmost importance. Only 13% of all patients have such operable lesions. When further eliminations are made from this potentially operable group because of poor surgical risk, age, or refusal of surgery, the percentage of all patients with prostatic cancer who undergo radical surgery is about 5 to 7% in most institutions. Radiotherapy in this group may yet achieve good results.

Stage III

Stage III carcinoma is probably not amenable to radical prostatectomy unless prior radiation or hormonal therapy has produced favorable tumor shrinkage. Radiation therapy appers to be the treatment of choice if the tumor is confined to the pelvis. The preliminary results of similar techniques from other institutions, although inconclusive, are highly encouraging. Complications of radiation therapy have been few and relatively minor. Orchiectomy or estrogen use or both are suitable alternative therapeutic regimens. With our current knowledge of lymphatic spread, lymphangiography may be valuable in determining both the choice of therapy and the portal size, should megavoltage radiotherapy be the chosen modality. With radiotherapy in stage III disease, the portals should probably be large enough to include the pelvic lymph nodes. In patients not qualifying for surgery or radiotherapy, the nodule may be observed until it progresses or antiandrogenic therapy is started.

Stage IV

Patients with metastatic or stage IV disease are treated antiandrogenically. Radiation therapy of localized painful metastasis is valuable. Radioactive phosphorus should be used only as a last resort in widespread painful bony metastasis.

John S. Harding, M.D.*
Roger E. Cupps, M D.†
David C. Utz, M.D.‡
Rochester, Minnesota

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*Mayo Graduate School of Medicine (University of Minnesota), Rochester: Resident in Radiology.

†Mayo Clinic and Mayo Foundation: Section of Therapeutic Radiology.

‡Mayo Clinic and Mayo Foundation: Section of Urology.

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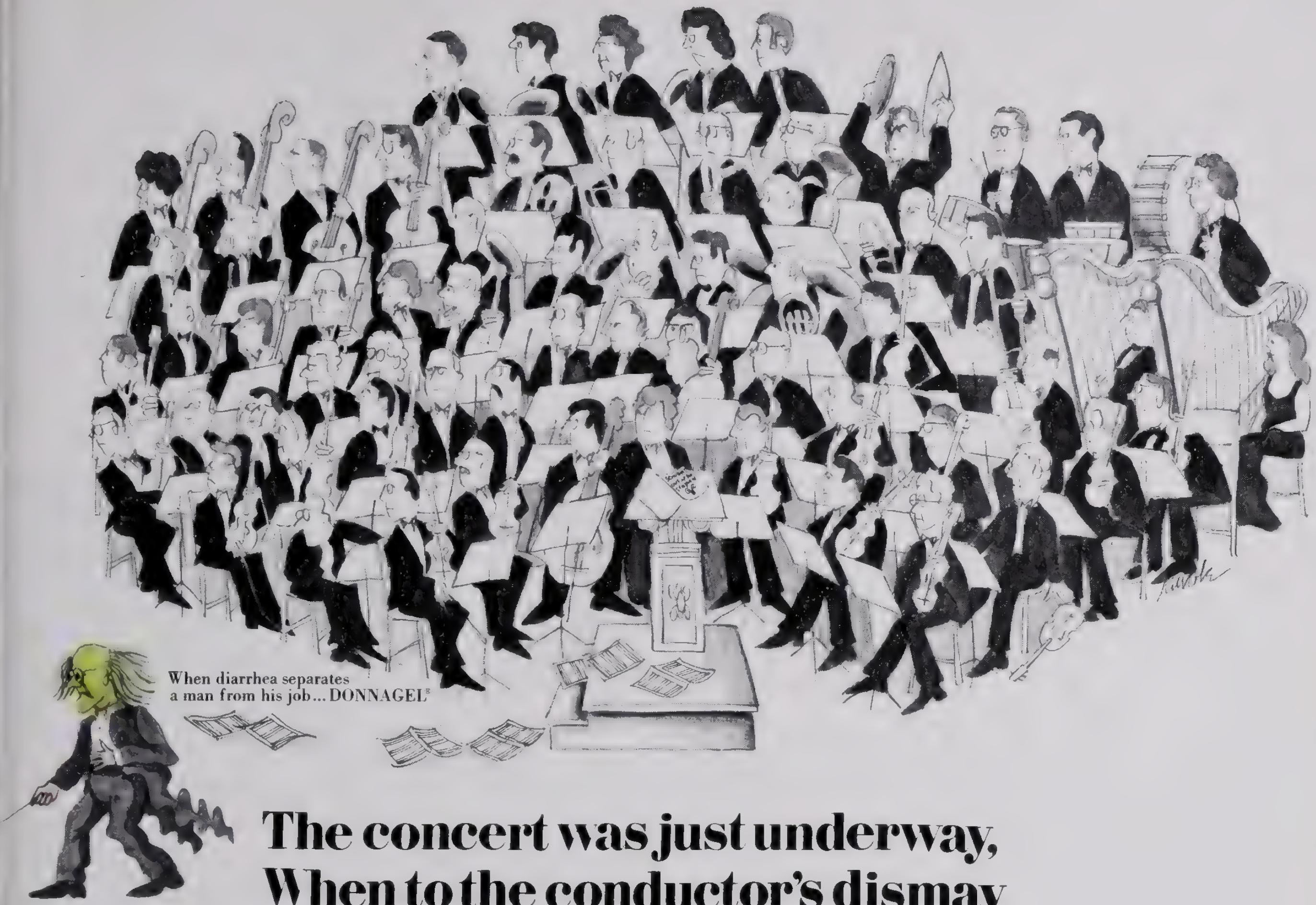
We are all miscarriages, but some miscarry at three months after conception and some at 100 years after birth.—Samuel Butler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(Continued to Page 1956)

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Continued from page 1955

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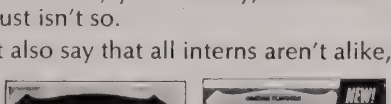

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Warnings: Administer cautiously to patients receiving phenothiazines or other CNS depressants or having history of convulsive seizures (See Adverse Reactions). Consider possibility of additive actions with alcohol or other psychotropic agents, particularly phenothiazines or MAO inhibitors.

Precautions: Avoid abrupt withdrawal after prolonged use, although withdrawal symptoms have not been reported to date. Exercise caution in addiction-prone individuals. If symptoms of hypersensitivity occur, discontinue at once and initiate appropriate symptomatic treatment. Avoid activities requiring optimal mental alertness if drowsiness or vertigo are present. As with any new drug, use cautiously in patients with history of drug allergies, blood dyscrasias, and hepatic or renal disease; periodic measurements of hepatic, hematopoietic and renal function should accompany prolonged and/or high doses.

Adverse Reactions: Most frequent reactions, rarely requiring discontinuation of tybamate, include drowsiness, dizziness, nausea, insomnia, and euphoria. There have been a few reports of skin rash, urticaria, and pruritus. Rare side effects include hyperactivity, fidgetiness, flushing, and tachycardia, suggesting excessive stimulation; also ataxia, unsteadiness, confusion, feeling of unreality, "panic reaction," fatigue, headache, paresthesias, vertigo, gastrointestinal disturbances, glossitis, and dry mouth. Grand mal or petit mal seizures have been reported in a few hospitalized psychotic patients receiving tybamate (up to 6000 mg. daily) together with phenothiazines and other psychotropic agents, but not with tybamate alone. Consider the possibility of rare, serious adverse reactions such as may occur with the related drug, meprobamate. If excessive amounts are ingested, gastric lavage and symptomatic therapy, including central stimulants as necessary, are recommended. Before prescribing, consult package circular.

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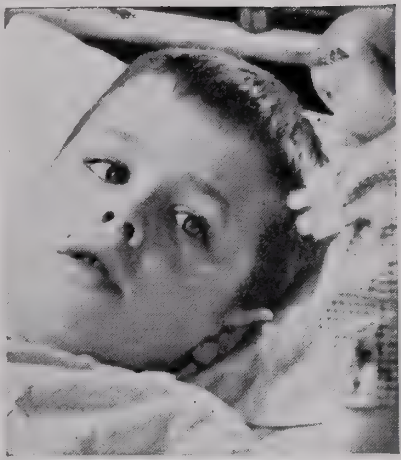

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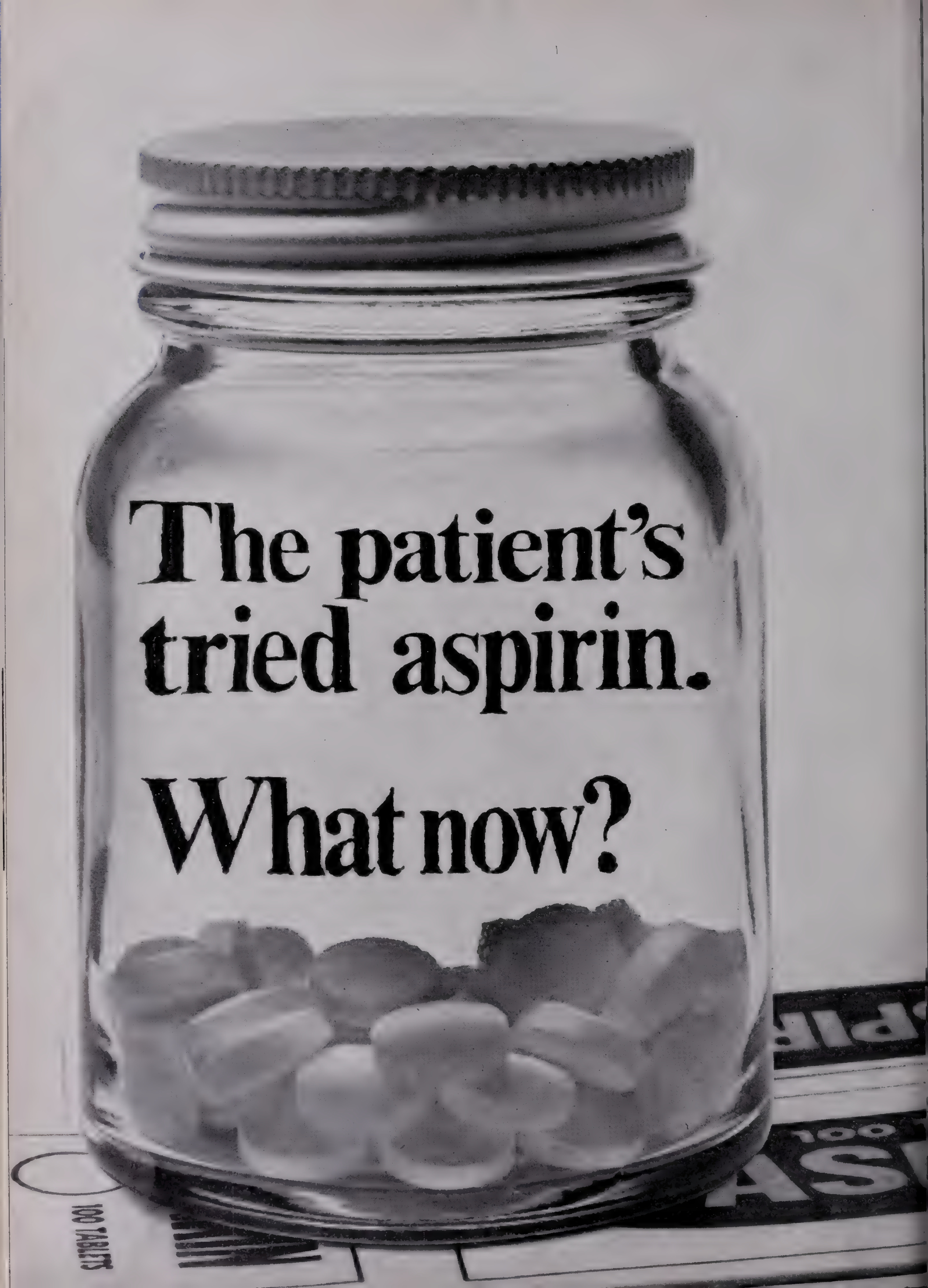
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Precautions: Keep out of reach of children. Not recommended for patients 12 years old or less. Carefully supervise dose and amounts prescribed, especially for patients prone to overdose themselves. Excessive prolonged use of meprobamate in susceptible persons—as alcoholics, ex-addicts, severe psychoneurotics—has resulted in dependence or habituation. Withdraw gradually after prolonged excessive dosage to avoid possibly severe withdrawal reactions including epileptiform seizures. Warn patients of possible reduced alcohol tolerance, with resultant slowed reactions and impaired judgment and coordination. If drowsiness, ataxia or visual disturbances (impairment of accommodation and visual acuity) occur, reduce dose. If symptoms persist, patients should not operate machinery or drive. After meprobamate overdose, prompt sleep, reduction of blood pressure, pulse and respiratory rates to basal levels, and hyperventilation are reported. Give cautiously and in small amounts to patients with suicidal tendencies. Treat attempted suicide (has resulted in coma, shock, vasomotor and respiratory collapse and anuria) with gastric lavage and appropriate symptomatic therapy (CNS stimulants and pressor amines as indicated). Two instances of accidental or intentional significant overdosage with ethoheptazine and aspirin have been reported. These were accompanied by CNS depression (drowsiness and lightheadedness) but resulted in uneventful recovery. On basis of pharmacologic data, CNS stimulation could be anticipated, with nausea, vomiting and salicylate intoxication (requires induced vomiting or gastric lavage, specific parenteral electrolyte therapy for ketoacidosis and dehydration, and observation for hypoprothrombinemic hemorrhage [usually requires whole blood transfusions]).

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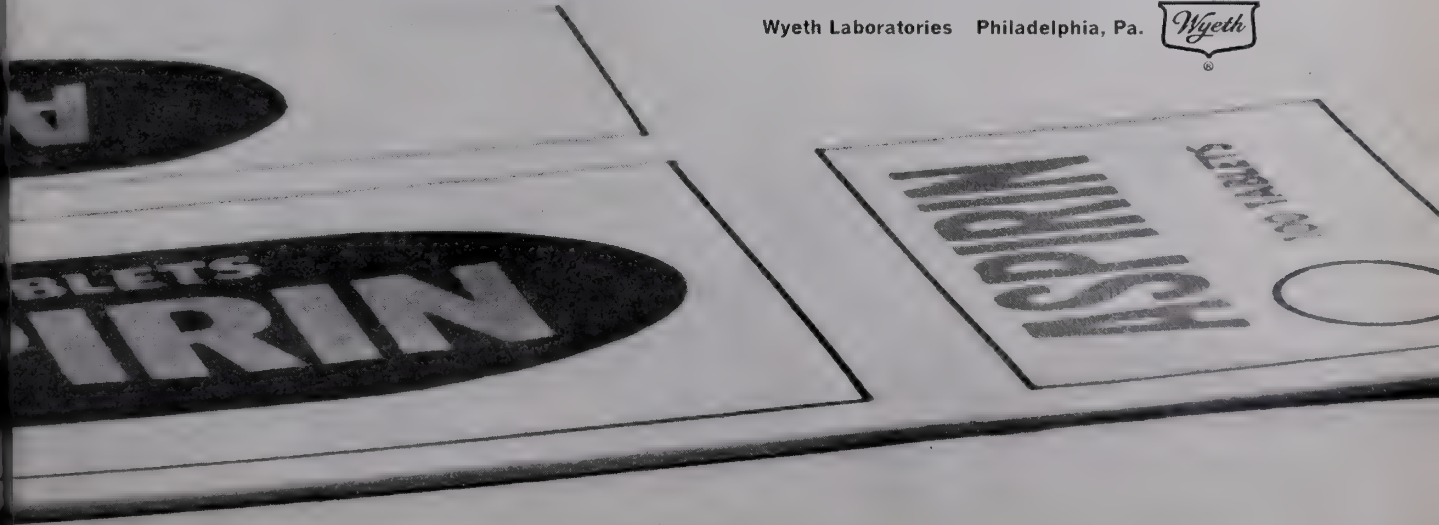

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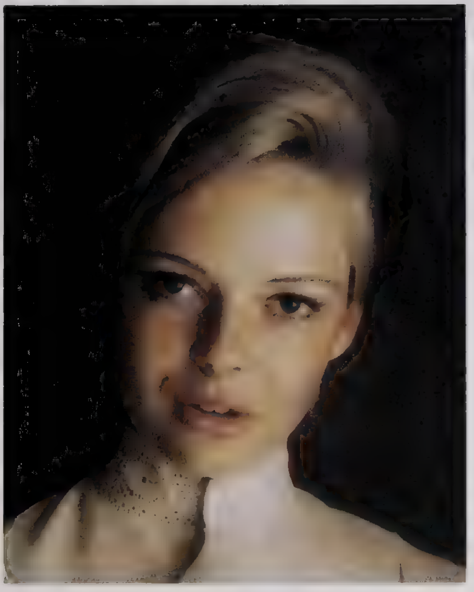

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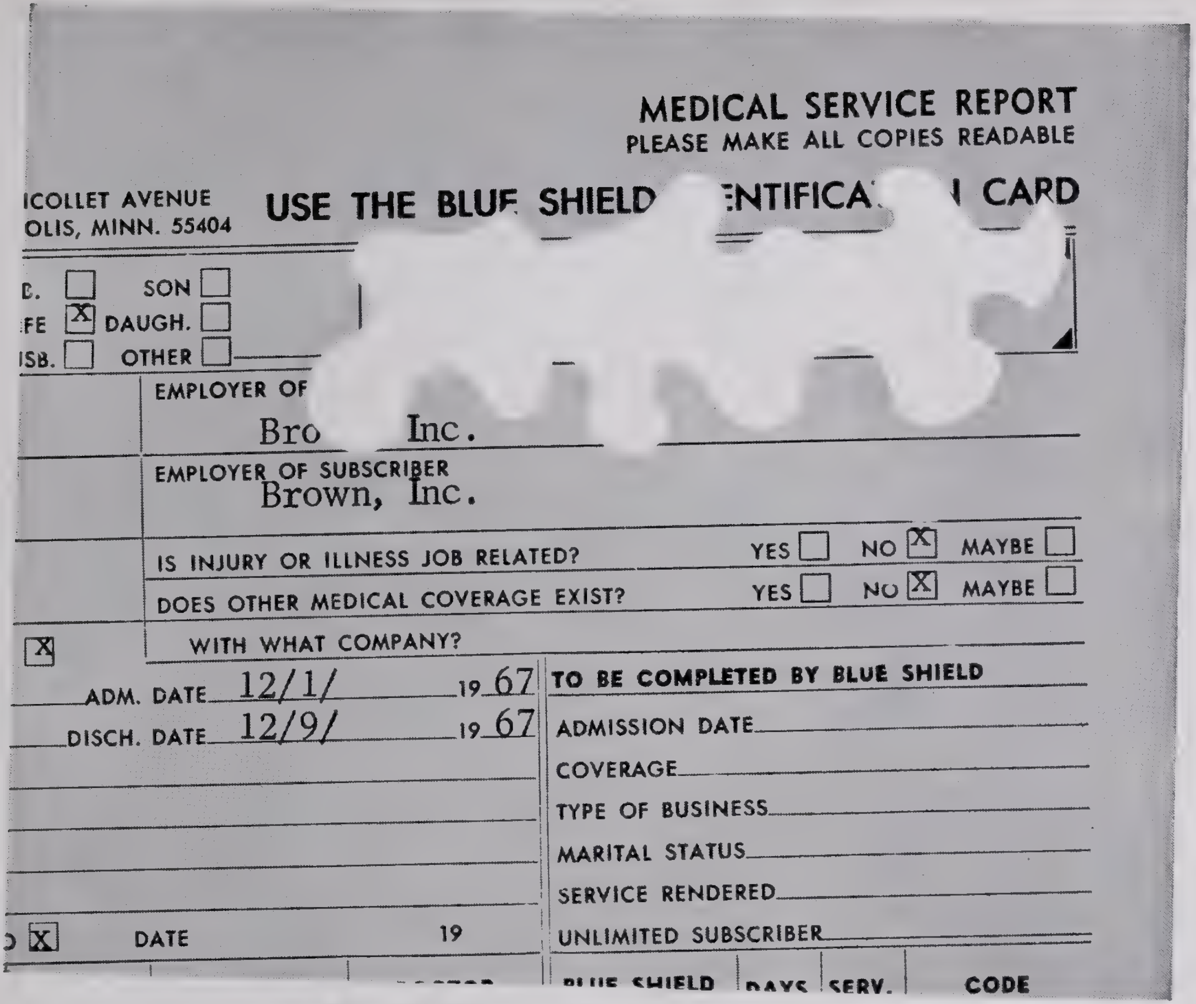

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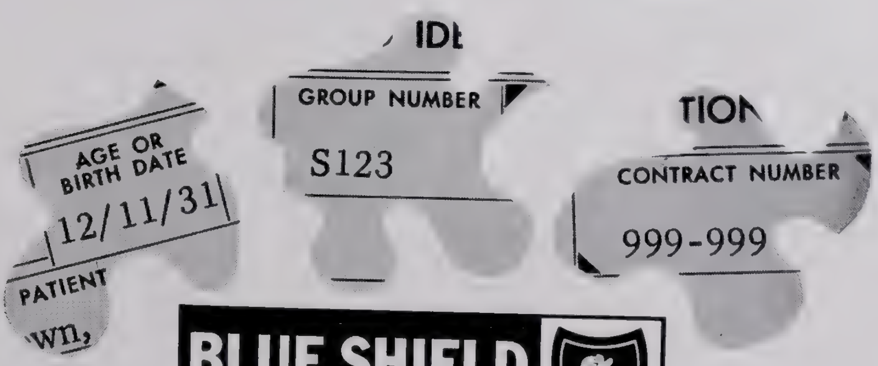

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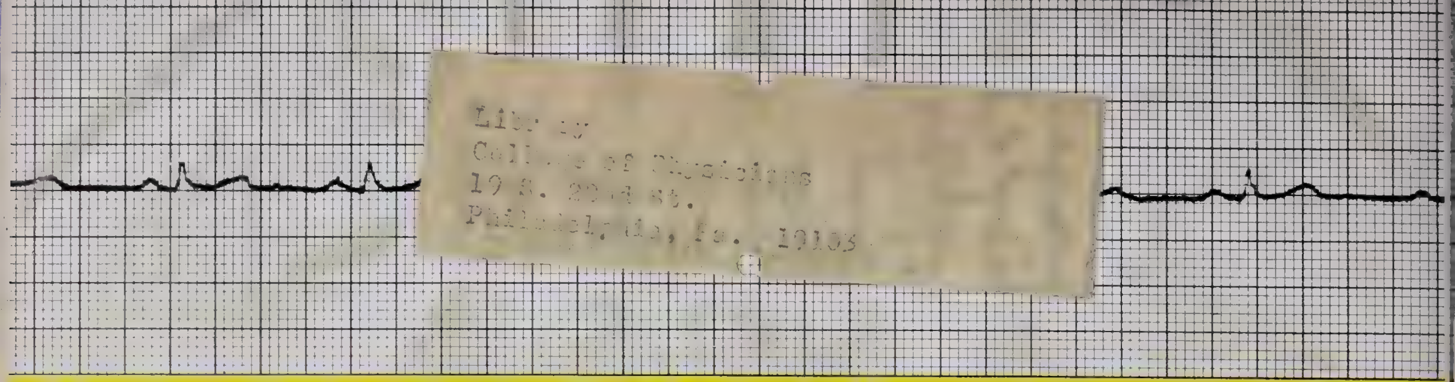

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Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms have occurred following abrupt discontinuance. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

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